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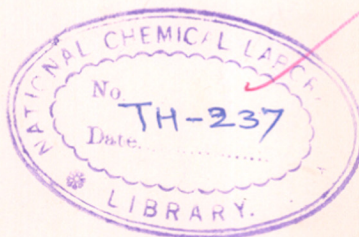


STUDIES IN HETEROCYCLIC CHEMISTRY: CHEMISTRY OF TRIHETEROATOMIC AZOLES

A THESIS
SUBMITTED TO THE
UNIVERSITY OF BOMBAY

COMPUTERISED

FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)



BY
GIRISH S. SHIRWAIKER
B. Sc. (Tech.)

547.79 (043)
SHI

NATIONAL CHEMICAL LABORATORY
POONA - 411 008 (INDIA)
APRIL 1979

TO MY PARENTS

STATEMENT REQUIRED TO BE SUBMITTED UNDER RULE 0.413 OF THE
UNIVERSITY OF BOMBAY

No part of this thesis has been submitted for a degree or diploma or other academic award. The literature concerning the problems investigated has been surveyed, and all the necessary references are given in the thesis. The present work has been clearly indicated separately. The experimental work has been carried out entirely by me. In accordance with the usual practice, due acknowledgement has been made wherever the work presented is based on the results of other workers.

R.B. Mitra

R.B. Mitra

R.B. Mitra
Research Guide

G.S. Shirwaiker

G.S. Shirwaiker

G.S. Shirwaiker
Candidate

GENERAL REMARKS

Spectral data: Ultraviolet spectra were taken in methanol on a Perkin-Elmer 350 spectrophotometer. Infrared spectra were recorded as nujol mulls, liq. films or chloroform solutions on a Perkin-Elmer Infracord 137 spectrophotometer with sodium chloride optics. The absorption values are recorded in cm^{-1} . ^1H nuclear magnetic resonance spectra were recorded on Varian T-60 spectrometer using tetramethyl silane as the internal standard. The chemical shift values are expressed in δ and the coupling constants (J) in Hz. Mass spectra were obtained with a CEC 21-110B double focussing mass spectrometer operating at 70 eV using a direct inlet system.

Temperatures are expressed in $^{\circ}\text{C}$. Melting points are uncorrected and have been taken in capillaries.

The figures underlined are the structure numbers and the figures shown in brackets are literature references. The numbers assigned to the structures given in each chapter refer only to that particular chapter. The list of references pertaining to each chapter has been given at the end of the chapter.

Abbreviations

Ar:	Aryl
Bz:	Benzoyl
CCl_4 :	Carbon tetrachloride
CDCl_3 :	Deuterated chloroform
d:	Doublet

DMAD:	Dimethyl acetylenedicarboxylate
DMF:	Dimethyl formamide
IR:	Infrared
KCN:	Potassium cyanide
M ⁺ :	Molecular ion
m:	Multiplet
m.p.:	Melting point
NMR:	Nuclear Magnetic Resonance
PCA:	Perchloric acid
Ph:	Phenyl
q	Quartet
R:	Alkyl or aralkyl
s:	Singlet
t:	Triplet
TFA:	Trifluoroacetic acid
TLC:	Thin Layer Chromatography
Ts:	p-Toluene sulfonyl
UV:	Ultraviolet

C O N T E N T S

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CHAPTER I

CYCLOADDITION REACTIONS OF SOME
TRIHETEROATOMIC AZOLES*

range of heterocyclic compounds, including nitrogen and sulfur heterocycles, and also a number of aromatic and heterocyclic compounds. The reaction of DMAD with a variety of heterocyclic compounds has been studied, and the results are summarized in Table I. The reaction of DMAD with a variety of heterocyclic compounds has been studied, and the results are summarized in Table I. The reaction of DMAD with a variety of heterocyclic compounds has been studied, and the results are summarized in Table I.

CYCLOADDUCTS OF DMAD WITH

AZAHETEROCYCLES-

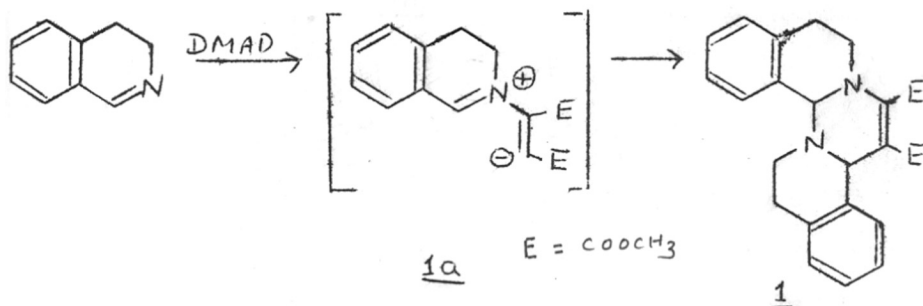
A BRIEF REVIEW

A wide range of heterocyclic compounds containing at least one nitrogen atom and possessing the grouping $-N = C(R) - \overline{R}$ where $\overline{R} = H$ or alkyl as a part of the ring are known to undergo cycloaddition reactions with dimethyl acetylenedicarboxylate (DMAD). Such cycloaddition reactions have been extensively studied with simple five and six membered heterocycles like pyrrole and pyridine and their fused benzo derivatives as well as compounds containing two heteroatoms such as thiazole, oxazole, imidazole, pyridazine, pyrimidine, pyrazine and their corresponding fused benzo derivatives. Depending on the nature of the heterocycle and the reaction conditions, the cycloaddition reaction of the above heterocycles with DMAD can lead to a variety of adducts with structures differing in the degree of complexity and incorporating 1 to 4 moles of DMAD with or without loss of the elements of a molecule of methanol. The extensive researches of Acheson and coworkers over the past two decades have greatly helped in unravelling some of the complex structures of these adducts and as a result mainly of their work, it is now possible to predict with a fair degree of confidence the structures of such adducts from the UV, IR, 1H NMR spectra together with the mass spectral fragmentation pattern. Besides, certain generalizations are now possible as to the mode of behaviour in adduct formation of these heterocycles.

Based on the number of moles of DMAD incorporated the cycloadducts can be broadly classified as 2:1, 1:1, 1:2, 1:3 and 1:4 molar adducts.

2:1 Adducts

Huisgen and Herbig (1) and thereafter Nair (2) reported that when DMAD is reacted with excess of 3,4-dihydroisoquinoline derivatives, the corresponding pyrimido[2,1-a:4,3-a]diisoquinoline derivatives 1 are formed. The reaction possibly proceeds by 1,4 dipolar cycloaddition of the initially formed 1:1 adduct 1a with the imine component present in excess.



A very small percentage of 2:1 molar adduct, yet unidentified, has been isolated from the reaction of indole with DMAD (3).

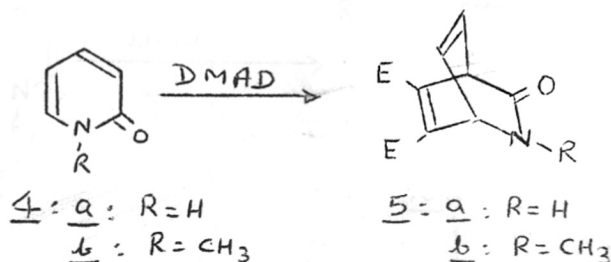
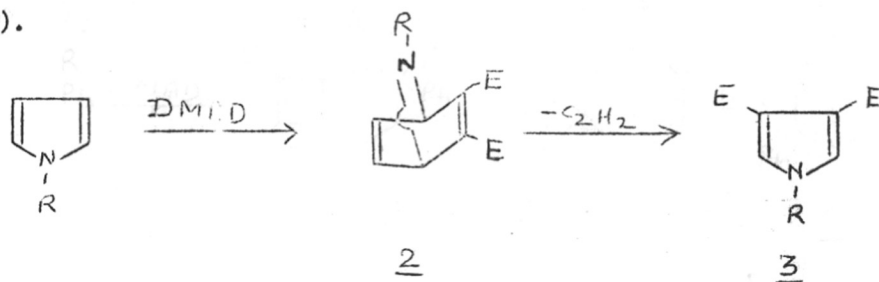
1:1 Adducts

These adducts can be classified into two types: one formed by simple Diels-Alder reactions of the heterocycles with DMAD and the second covering the rest.

A: Diels Alder type of 1:1 Adducts

A small number of pyrroles undergo 2,5 cycloaddition reactions with DMAD in Diels Alder fashion to yield the respective 1:1 adducts 2; these spontaneously or thermally lose a molecule of acetylene to form carboxylated pyrrole derivatives.

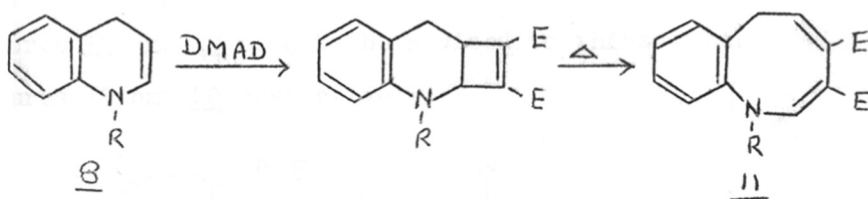
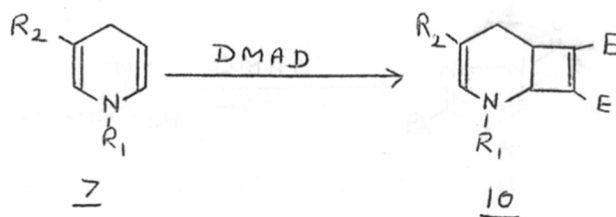
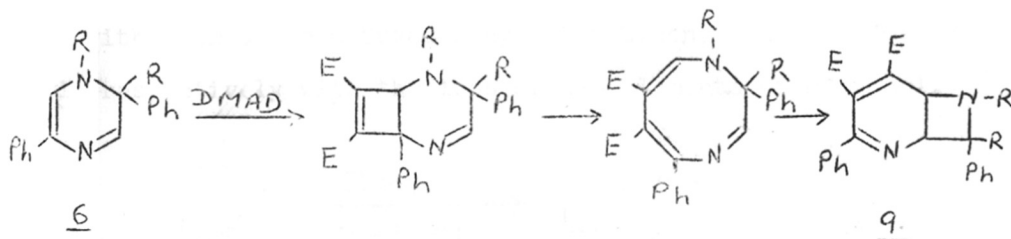
3 (4).



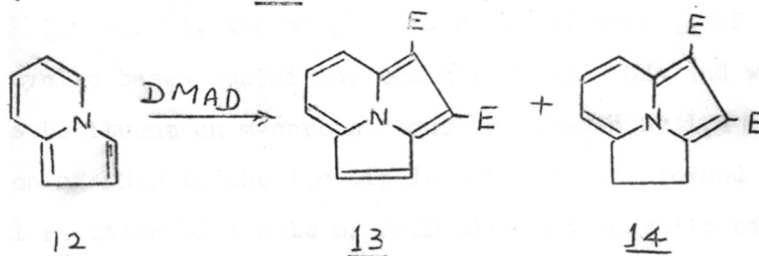
The reaction of 2-pyridone 4a with DMAD gives the Diels Alder adduct 5a in minor proportions while 1-methyl-2-pyridone 4b with DMAD mainly produces the corresponding Diels Alder adduct 5b(5). Oxazole derivatives also give Diels Alder adducts with DMAD (5a).

B:1:1 Adducts - Other than Diels Alder type

Enaminic heterocyclic bases like 1,2-dihydropyrazines 6 (6), 1,4-dihydropyridines 7 (7), 1,4-dihydroquinolines 8 (8) etc. cycloadd with DMAD in 2 + 2 fashion to give 1:1 adducts 9, 10 and 11 respectively, containing the fused cyclobutene ring system.

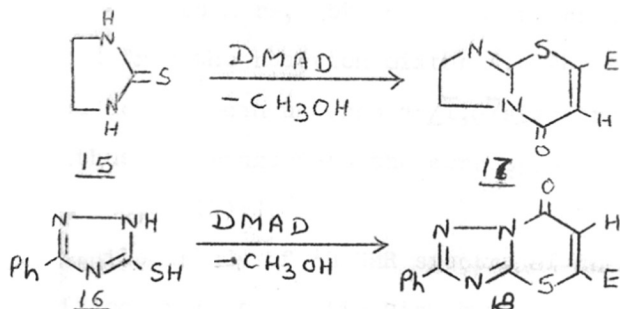


Indolizine 12 (9) combines with DMAD in presence of palladium-charcoal to produce dimethyl cycl [3.2.2]azine-1,2-dicarboxylate 13 along with small amounts of the corresponding 3,4-dihydro derivative 14.

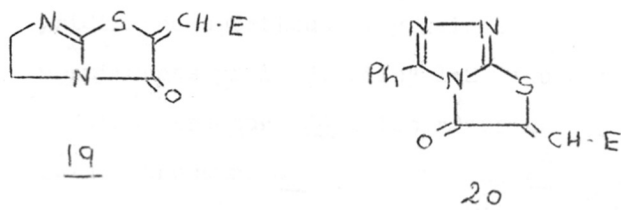


Cyclic thiureas like imidazolidinethione 15 (10), 3-mercapto-5-phenyl-1,2,4-triazole 16 (11) have been reported to

react with DMAD to form fused dihydrothiazinone ring systems 17 and 18 respectively with the loss of the elements of methanol.

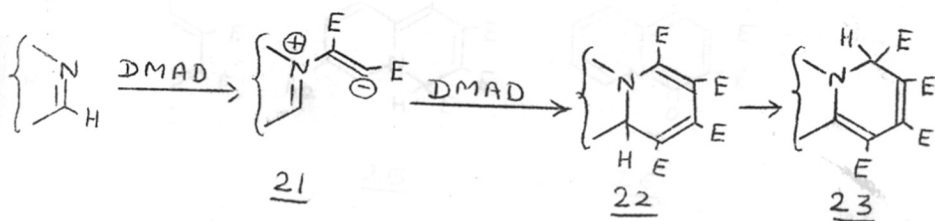


However, based on the spectral data and recent revision of the structures of addition products formed from thioureas and DMAD by X-ray crystallography (12), these dihydrothiazinone structures 17 and 18 need to be revised to thiazolinone structures 19 and 20 respectively.



1: 2 Adducts

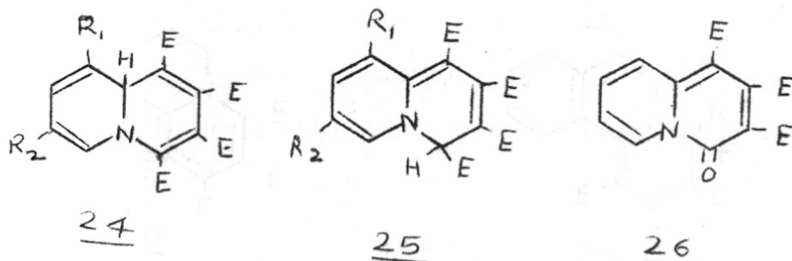
In general, the simple 1:2 cyclo-adducts 22 of DMAD with heterocyclic bases containing the moiety $-\text{N}=\text{CH}-$ and without any alkyl substituent on α -carbon atoms are formed by 1,4 cyclo-addition of DMAD to the 1,4 dipole 21 which is formed by the initial reaction of 1 mole of DMAD with heterocyclic base.



But this simple 1:2 cycloadduct 22, in a vast number of cases is found to be unstable or "labile" and so along with this, some other isomers, obtainable by rearrangement of 22, are isolated from the reaction mixtures. The simple 1:2 "labile" adducts 22 can undergo a $\overline{1,5}$ sigmatropic hydrogen shift and thus rearrange into the corresponding 1:2 "stable" adducts 23 (13,14,15).

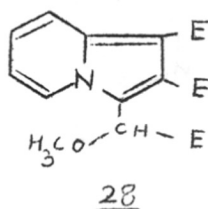
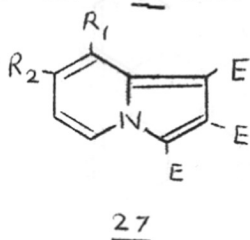
Detailed study of ^1H NMR spectra of these adducts has now made it possible to distinguish between "labile" and "stable" adducts based on the chemical shift values of the bridgehead proton or 4-H proton. The bridgehead proton in "labile" adducts exhibits a sharp singlet at ca. 65.0 while the 4-H proton in "stable" adducts is shown as a singlet at ca. 66.0 (26).

Pyridine and substituted pyridines lacking in α -alkyl substituents yield "labile" 1:2 adducts with a 9aH-quinolizine structure 24 which rearrange to a "stable" 4H-quinolizine structure 25 via a facile $\overline{1,5}$ sigmatropic hydrogen shift (13). For pyridine itself the "labile" adduct 24 ($R_1 = R_2 = \text{H}$) is difficult to isolate, but with β -picoline and 3,5-dimethyl-pyridine, the corresponding "labile" adducts 24 ($\overline{R}_1 = \text{CH}_3$, $R_2 = \text{H}$ and $R_1 = R_2 = \text{CH}_3$ respectively) have been isolated (14,15).

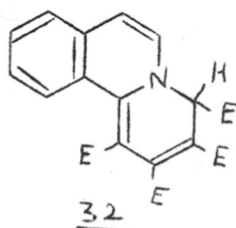
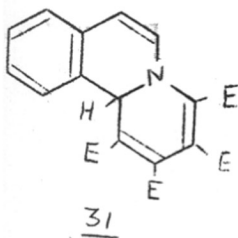
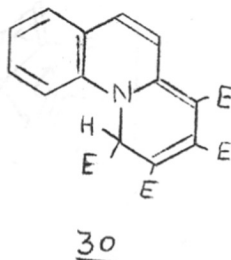
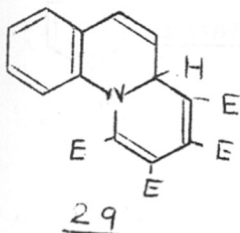


An unusual 1:2 adduct 26, "Kashimoto's Compound", is formed as a minor product of the reaction between DMAD and pyridine with loss of elements of methanol; a homolog is obtained from β -picoline (15).

When the reaction of pyridine or β -picoline with DMAD is carried out in methanol, the corresponding indolizine derivative 27 [$R_1 = R_2 = H$] and the methoxy methyl indolizine derivatives 28 have been isolated from the reaction mixture (16).

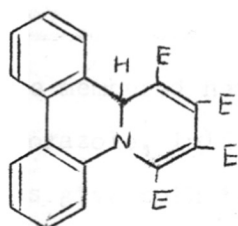
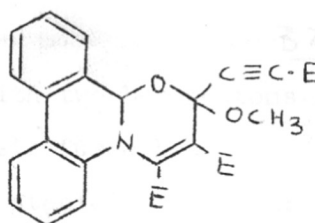


Quinoline, isoquinoline and their substituted derivatives also give both 'labile' and 'stable' type of adducts. The 'labile' adduct 29 from quinoline easily isomerizes to the 'stable' adduct 30, but with isoquinoline, the 'labile' adduct 31 is much less readily isomerized, boiling xylene or sulfuric-acetic acid treatment being required to convert it to 32 (17,18).

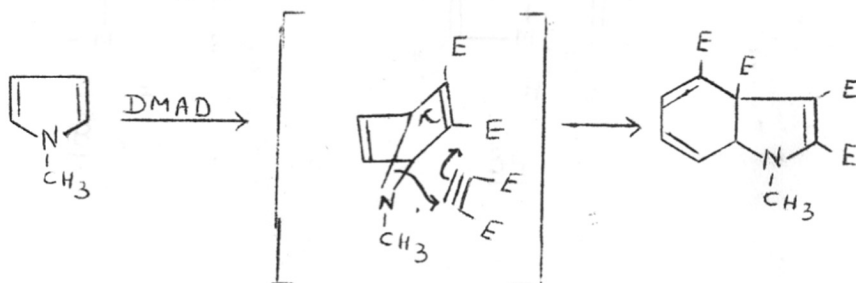


Compound 27 [$R_1 - R_2 = o-C_6H_4$] has been isolated from the reaction of DMAD with isoquinoline using methanol as a solvent (19).

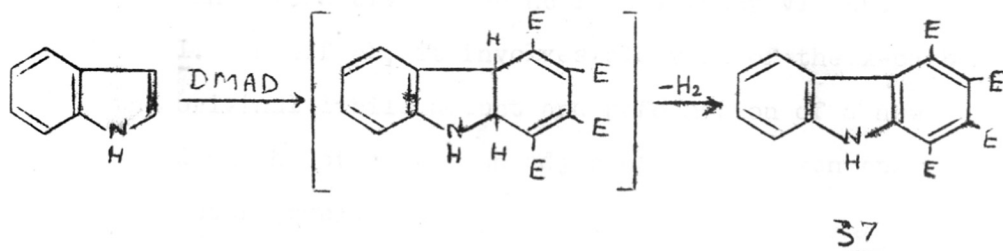
Reaction of phenanthridine with DMAD yields the usual 1:2 "labile" adduct 33 along with minor quantities of an unusual 1:2 adduct 34 (20).

3334

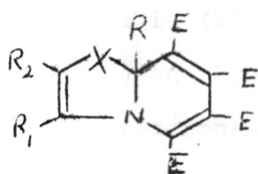
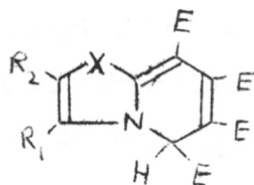
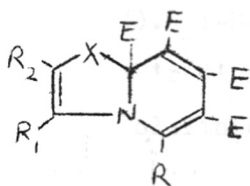
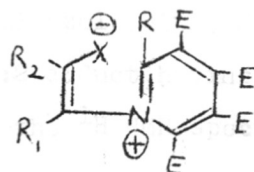
1-Methyl-pyrrole and DMAD interact at 0° to give a 1:2 adduct 36, possibly formed by addition of the ester across the 2,7 positions of the Diels Alder adduct 35 (not isolated) formed initially (21).

3536

Indole, on standing with DMAD for 74 days gives a good yield of carbazole 37, which is expected to be formed by dehydrogenation of the 1:2 'labile' adduct (3).

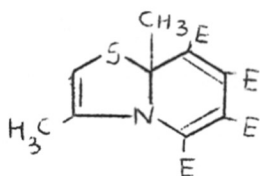
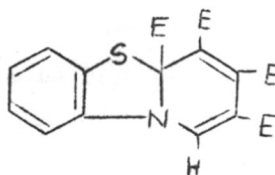


Five membered heterocycles with two heteroatoms such as thiazole, oxazole, imidazole and their fused benzo derivatives give both 'labile' and 'stable' type of 1:2 adducts. The labile adducts 38 [$\bar{X} = S, NR'$] from thiazole and imidazole derivatives besides isomerising to the corresponding 'stable' adducts 39 [$\bar{X} = S, NR'$], can rearrange to compounds of the type 40 [$\bar{X} = S, NR'$].

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Compound 40 can be formed from 38 by a rearrangement proceeding via a concerted $[1,5]$ suprafacial sigmatropic shift which might be thermally allowed for an atom with non bonded electrons or an alternative non-concerted pathway via the zwitterion 41. In effect, it involves cleavage of the X-carbon bond in the original labile adduct and reformation of a new X-carbon bond on the other carbon adjacent to nitrogen and carrying an ester group.

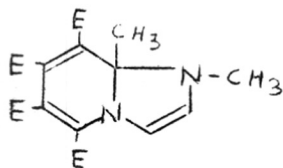
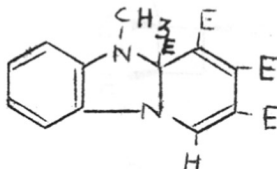
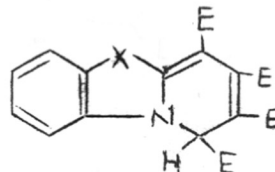
The 2,4-dimethylthiazole adduct 42 is the only 'labile' type of adduct isolated so far for this heterocycle (22,23).

4243

Thiazole (23,24), its 2-methyl (23), 4-methyl (23,24), 5-methyl (22) and 2,5-dimethyl (22) derivatives react with DMAD to give the rearranged adducts of the type 40. Benzothiazole furnishes as major product, the rearranged adduct 43 with DMAD in absence of solvent or in acetonitrile, dimethyl formamide $[DMF]$ or toluene (22,24).

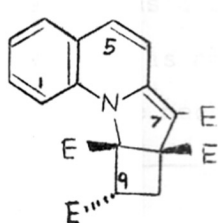
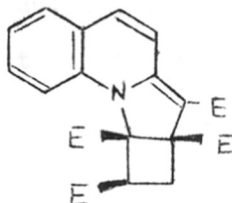
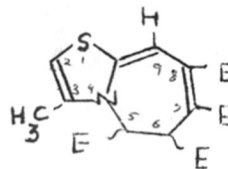
1,2-Dimethyl-imidazole reacts with DMAD to give the 1:2 adduct 44 (25). 1-Methyl-benzimidazole with DMAD, on the other hand, gives a 'red' rearranged 1:2 adduct having structure 45 (26). The olefinic proton in the 1H NMR spectra of adducts

40 ($R = H$), 43 and 45 (9H) appear as a singlet around δ 8.50, which is quite characteristic of their structures (22).

444546: $X = S$ 47: $X = O$ 48: $X = NCH_3$

The stable type of adducts with these heterocycles is represented by structures 46, 47 and 48 (22) for benzothiazole, benzoxazole and 1-methyl-benzimidazole respectively, the formation of which involves a $[1,5]$ sigmatropic hydrogen shift as in the case of quinolizines 25, 30 and 32. In such adducts, the 9H proton appears characteristically at δ 6.2 - 6.4.

Heterocycles containing the grouping $-N = C(R) -$ ($\bar{R} = CH_3$, or $-CH_2-$) with an active 2-alkyl substituent give with DMAD, 1:2 adducts of more complex structures, besides the above type of adducts. These complex adducts fall mainly into 3 categories. Thus, 2-methylquinoline and its derivatives give two types of adducts represented by the tetrahydrocyclobutapyrrole structures 49 and 50 which were finally settled by X-ray crystallography and confirmed by ^{13}C NMR spectroscopy (27).

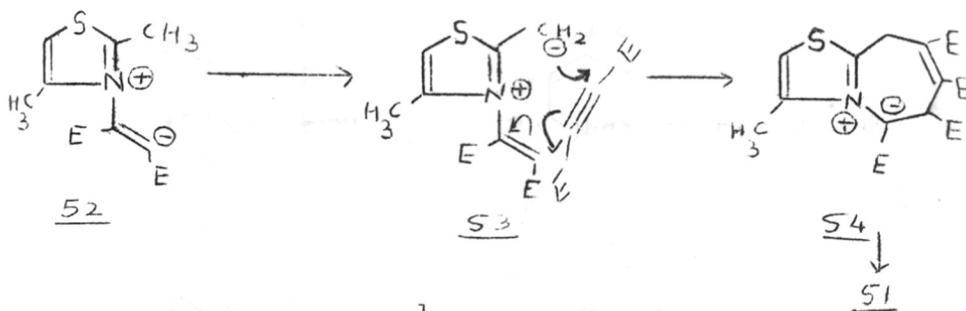
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The formation of 49 and 50 involves complex rearrangements of the initially formed adducts since ^{13}C tracer studies have indicated that the original 2-methyl substituent of quinoline ends up as a $\text{C}_8 - \text{CH}_2 -$ group in the final product (28). The mechanism is still unknown. The ^1H NMR spectra of these type of adducts show either an ABC system or an AB system with one low field proton. Adducts of the type 49 and 50 can be distinguished on the basis of their ^1H NMR spectra; 1-H and 9-ester methyl signals in adducts of the type 49 appear at high field whereas in adducts of the type 50 the corresponding protons appear in the normal ranges (29). The mass spectral fragmentation pattern of these adducts is highly characteristic since they both lose the elements of methyl acrylate or its equivalent to give an intense $\text{M}^+ - 86$ ion peak (27,30).

The third type of adduct from heterocycles possessing activated methyl or methylene groups at α -positions is a dihydroazepine derivative represented by 51 for 2^{4di}-methyl-thiazole (24). The ^1H NMR spectra of this type of adducts are quite characteristic, the enaminic olefinic α -H proton

appearing as a singlet at ca. δ 5.20 and the ^5H , ^6H protons showing up as an AB quartet around δ 5.40 - 6.00 with $J = 6$ Hz.

The mechanism of formation of 51 is outlined in 52 $\longrightarrow$ 54 $\longrightarrow$ 51.

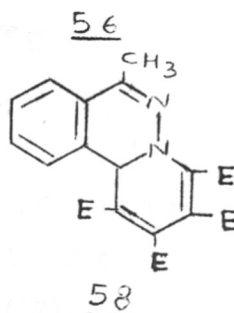
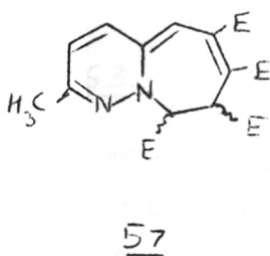
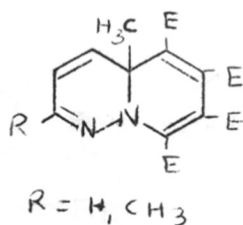
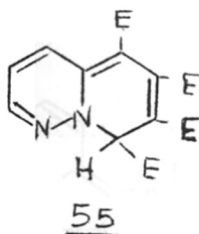


Thus based on the ^1H NMR spectra and mass spectral fragmentation pattern, it is now possible to define precisely the correct structures for complex 1:2 adducts. The adducts containing a tetrahydrocyclobutapyrrole ring system lose methyl acrylate or an equivalent fragment in the mass spectrometer and ^1H NMR spectrum show either an ABC system or an AB system with one low field proton. However, the dihydroazepine type of adducts lose primarily the ester groups in the mass spectrometer and show a low field AB system with a high field singlet for the enaminic proton in the ^1H NMR spectra.

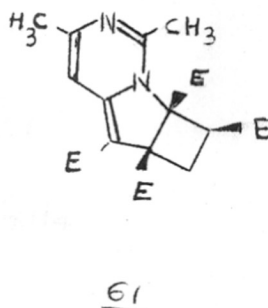
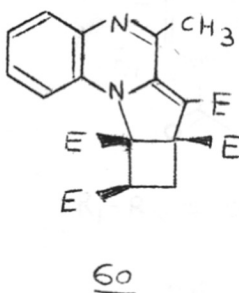
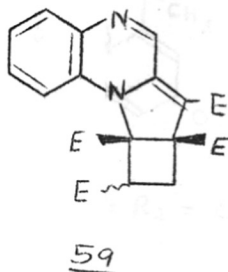
Six membered heterocycles containing two heteroatoms like pyridazine, pyrimidine, pyrazine and their fused benzo derivatives with DMAD give different type of 1:2 adducts discussed above.

Pyridazine reacts with DMAD to produce the 'stable' adduct 55 while 'labile' adducts 56 are obtainable from

3-methyl and 3,6-dimethyl-pyridazine (31). The major product isolated from the reaction of 3,6-dimethyl-pyridazine with DMAD is dihydroazepine adduct 57 (31); however repetition of the reaction gave only tetrahydrocyclobutapyrrole type of adducts (27).

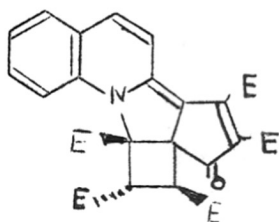
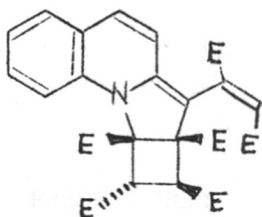
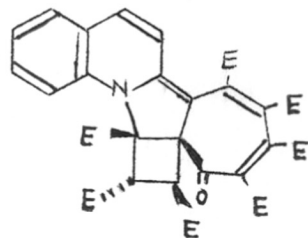


1-Methylphthalazine gives only the 'labile' adduct 58 with DMAD (31). 2-Methylquinoxaline gives with DMAD both the stereoisomers of 59 while with 2,3-dimethylquinoxaline only 60 has been isolated (32). Similarly 2,4,6-trimethylpyrimidine gives 61 with DMAD (33).

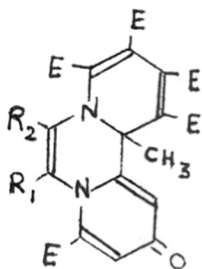
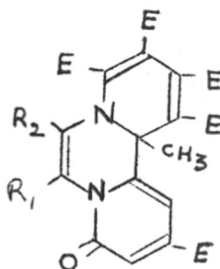


1:3 and 1:4 Adducts

2-Methyl substituted quinolines are known to give red 1:3 adducts with DMAD (34). The red 1:3 adduct from 2,8-dimethyl-quinoline and DMAD has been shown to be 62 (35) by X-ray crystallography.

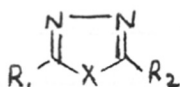
636264

Compounds 63 and 64 are formed in the reaction of quinoline with DMAD by 1:3 and 1:4 addition of the ester with the loss of elements of methanol (27). 2,3,5,6-Tetramethylpyrazine (33) and 2,3-dimethyl-quinoxaline (32) also give 1:3 adducts with DMAD with proposed structures of either 65 or 66.

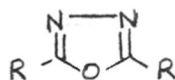
6566

PRESENT WORK

Because of the variety of adducts obtained in the various cycloaddition reactions of a large number of heterocycles with different dienophiles or dipolarophiles like DMAD, phenyl isocyanate, phenyl isothiocyanate and their mixtures, it was felt that a study of the cycloaddition reactions of above dienophiles with symmetrical triheteroatomic azoles such as 1,3,4-oxadiazoles, 1,3,4 thiadiazoles and 1,2,4-triazoles $\underline{67}$ $\angle \bar{X} = O, S, NMe \text{ resp.}$ could be quite rewarding.



67

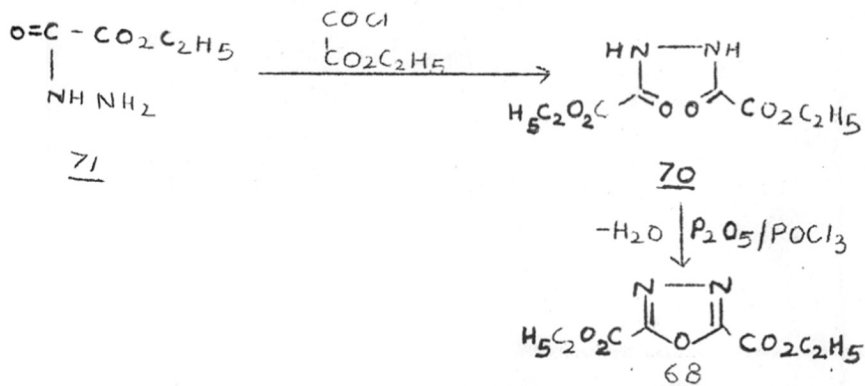


68: $R = CO_2C_2H_5$

69: $R = Ph$

It is expected that the basicity of the nitrogen atoms would be least in oxadiazoles and maximum in triazoles among these heterocycles. The groups (R_1, R_2) at the α -positions of X in 67 also have significant effect on the nucleophilicity of nitrogens. Thus, due to the electrophilicity of carbethoxy and phenyl groups, both 2,5-dicarbethoxy-1,3,4-oxadiazole 68 and 2,5-diphenyl-1,3,4-oxadiazole 69 (36) did not react with DMAD even at 200° , the starting materials being recovered back from the reaction mixtures. Compound 68 was prepared by cyclo-dehydration of diethyl hydrazino dioxalate 70 with $P_2O_5/POCl_3$ mixture (37); Compound 70 was prepared by the action of ethyl

oxalyl chloride on ethyl hydrazino oxalate 71 (38).



Reaction of 2-phenyl-1,3,4-oxadiazole and 2-phenyl-1,3,4-thiadiazole with DMAD

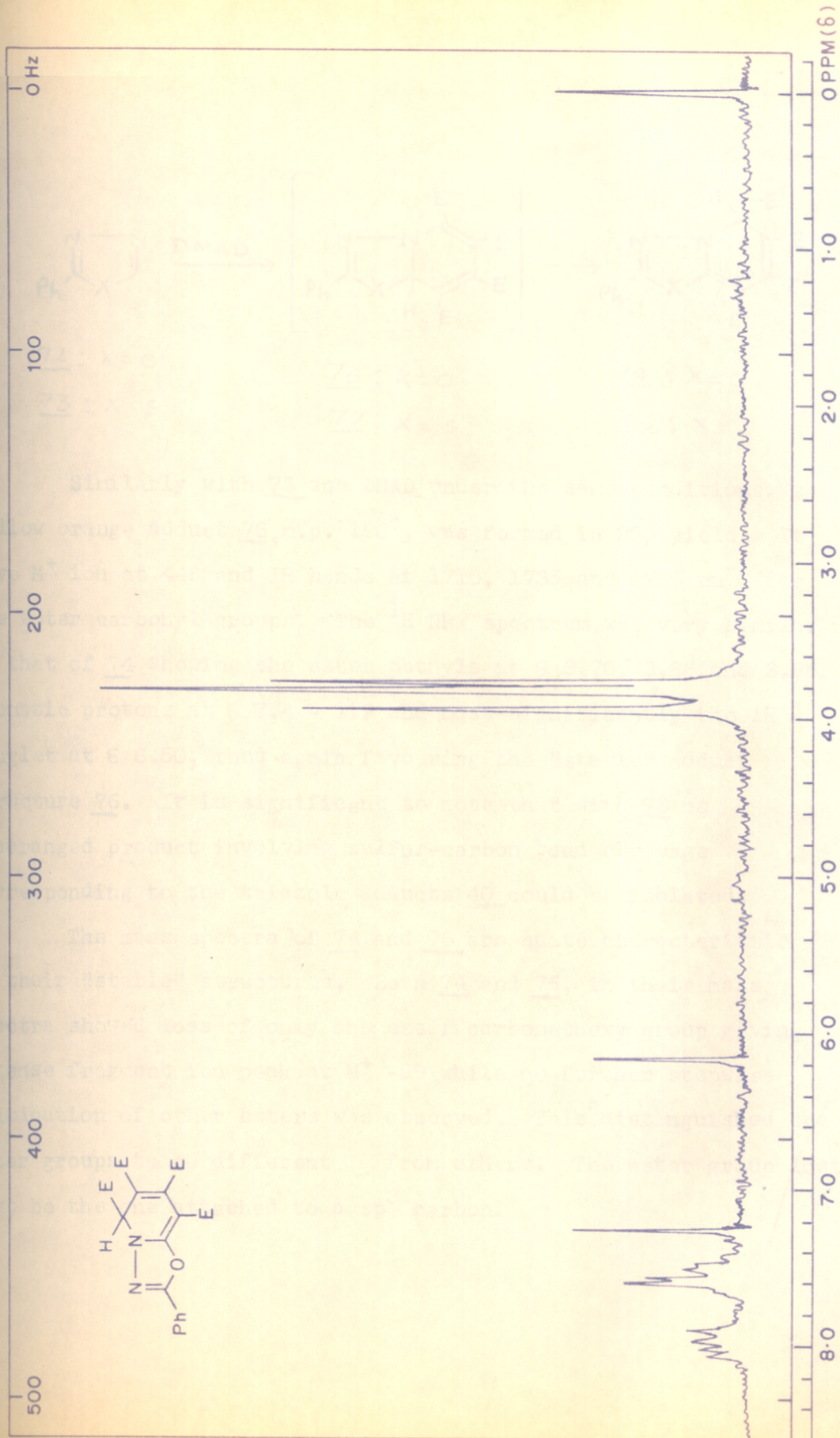
In order to permit one of the nitrogens to be sufficiently nucleophilic to react with DMAD, the 5-unsubstituted 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives viz. 2-phenyl-1,3,4-oxadiazole 72 (39) and 2-phenyl-1,3,4-thiadiazole 73 (40) were selected for the reaction.

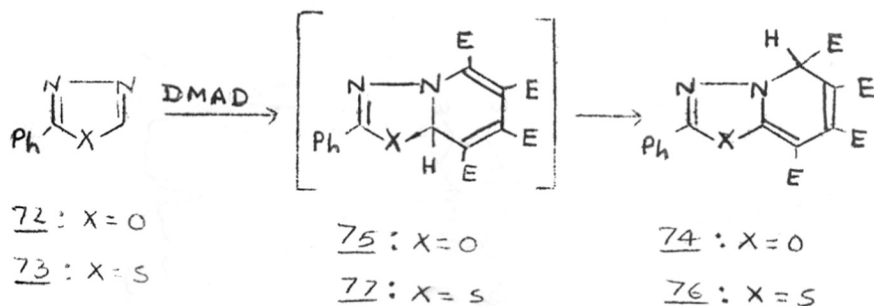
The reaction of 72 with 2 moles of DMAD neat at 140° for 3 hr. gave pyridino (2,1-b) 1,3,4-oxadiazole derivative 74, m.p. 192°, in 50% yield. It showed M⁺ ion at 430 and IR carbonyl bands at 1700 and 1745 cm⁻¹ for α,β-unsaturated and saturated ester carbonyls respectively. In the ¹H NMR spectrum, apart from four ester methyls at δ 3.80, 3.86 and 4.0 and aromatic protons at δ 7.33- 8.0, it showed a 1H singlet at δ 6.20, indicating the "stable" 1:2 adduct structure 74, and not the "labile" structure 75 for the compound.

547.79(043)

SHI

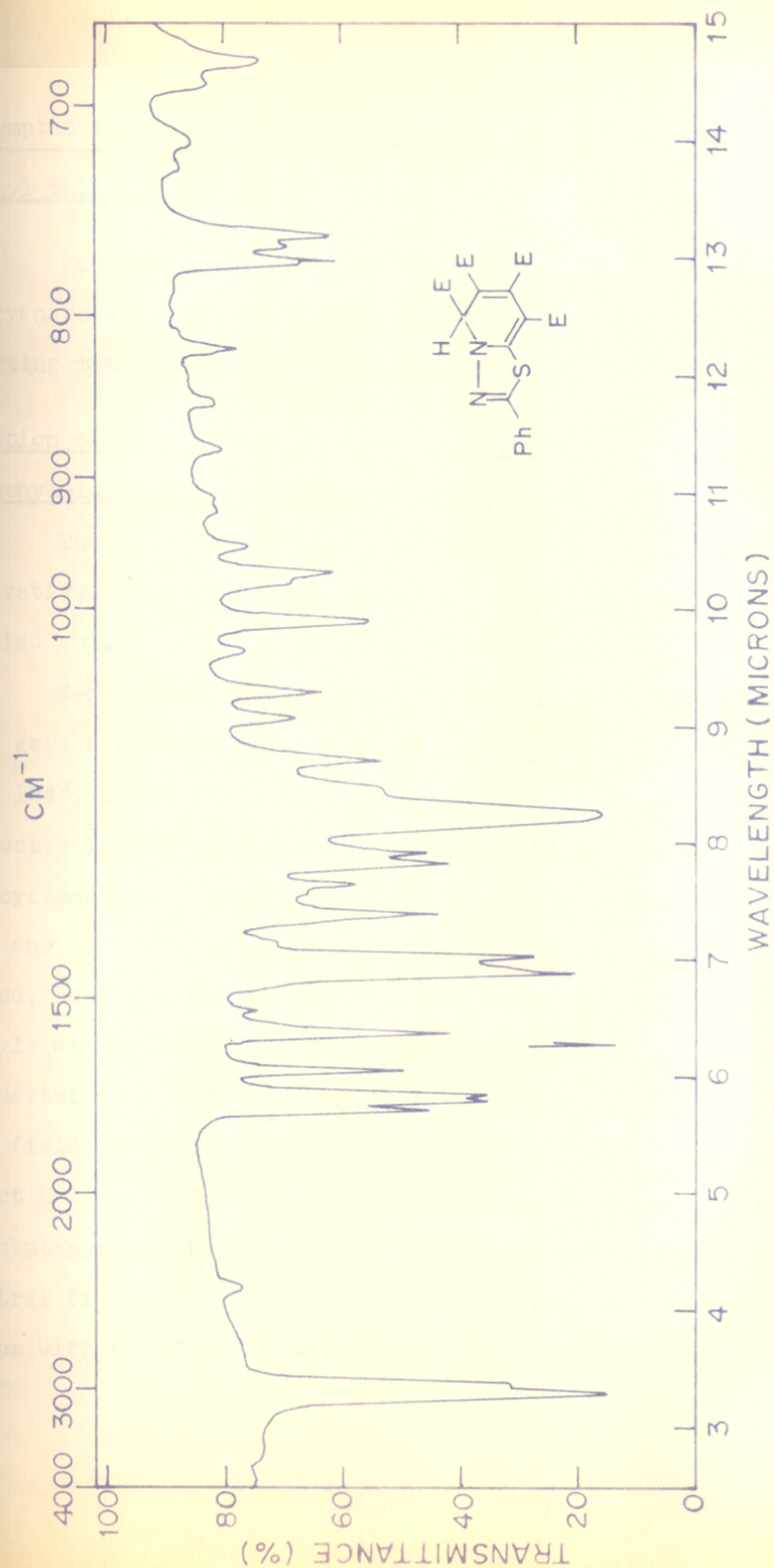
SUMMARY





Similarly with 73 and DMAD under the same conditions, the yellow orange adduct 76, m.p. 196° , was formed in 25% yield. It gave M^{+} ion at 446 and IR bands at 1710, 1735 and 1750 cm^{-1} for the ester carbonyl groups. The ^1H NMR spectrum was very similar to that of 74 showing the ester methyls at δ 3.76, 3.86 and 3.96, aromatic protons at δ 7.4 - 7.9 and most significantly the ^1H singlet at δ 6.50, thus again favouring the "stable" adduct structure 76. It is significant to note that with 73 no rearranged product involving sulfur-carbon bond cleavage corresponding to the thiazole adducts 40 could be isolated.

The mass spectra of 74 and 76 are quite characteristic of their "stable" structures. Both 74 and 76, in their mass spectra showed loss of only one ester carbomethoxy group giving intense fragment ion peak at $\text{M}^{+} - 59$ while no further stepwise elimination of other esters was observed. This distinguished one ester groups to be different from others. The ester group lost must be the one attached to a sp^3 carbon.

IR OF COMPOUND 76

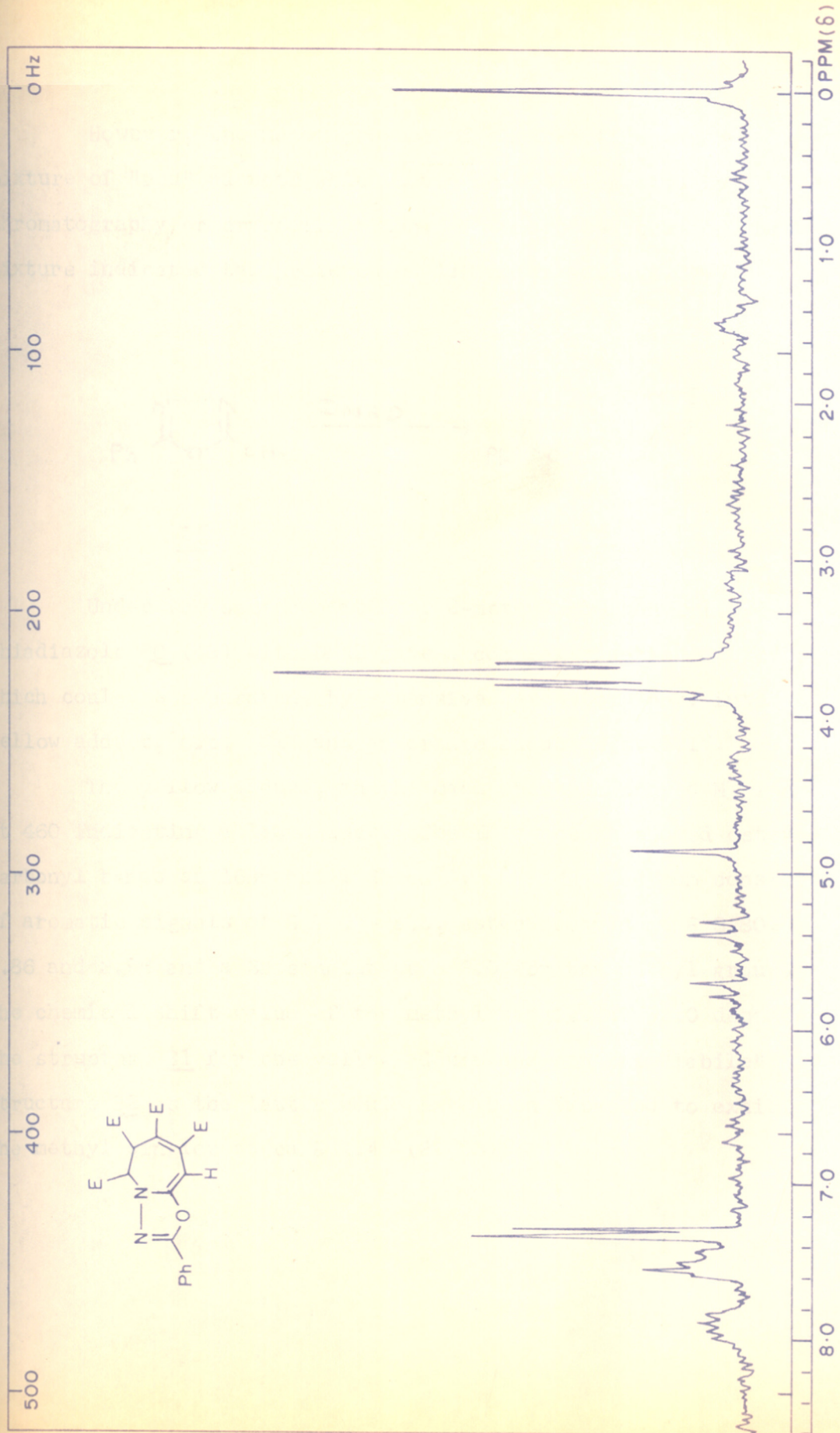
Attempted reactions of 72 and 73 with phenyl isocyanate and phenyl isothiocyanate

Compounds 72 and 73 did not react with both phenyl isocyanate and phenyl isothiocyanate even at 140° for 5 hr, the starting materials being recovered from the reaction mixtures.

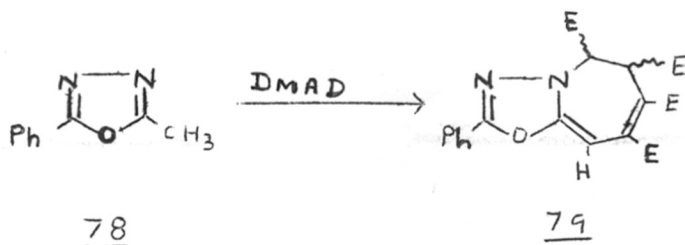
Reaction of 2-methyl-5-phenyl-1,3,4-oxadiazole and 2-methyl-5-phenyl-1,3,4-thiadiazole with DMAD

The reactions of 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives containing an activated methyl group at 2-position were carried out.

2-Methyl-5-phenyl-1,3,4-oxadiazole 78 (41) with DMAD at 100° gave a mixture of products from which an orange adduct, m.p. 134° , could be isolated by column chromatography as a minor product. In the mass spectrum, it gave M^{+} ion at 444, indicating a 1:2 cycloadduct. The IR spectrum showed carbonyl bands at 1700, 1740 and 1750 cm^{-1} for the ester groups. The ^1H NMR spectrum showed, besides the aromatic protons at δ 7.3 - 8.1 and ester methyls at δ 3.66, 3.73, 3.80 and 3.86, a 1H singlet at δ 4.90 and an AB quartet at δ 5.36 and δ 5.83 ($J = 5\text{ Hz}$). Thus, the presence of a high field 1H singlet with low field AB quartet indicated that the adduct has a dihydroazepine type structure 79, and not tetrahydro-cyclobutapyrrole type structure. This is supported by the mass spectral fragmentation pattern which showed only loss of ester groups with no $M^{+} - 86$ peak.

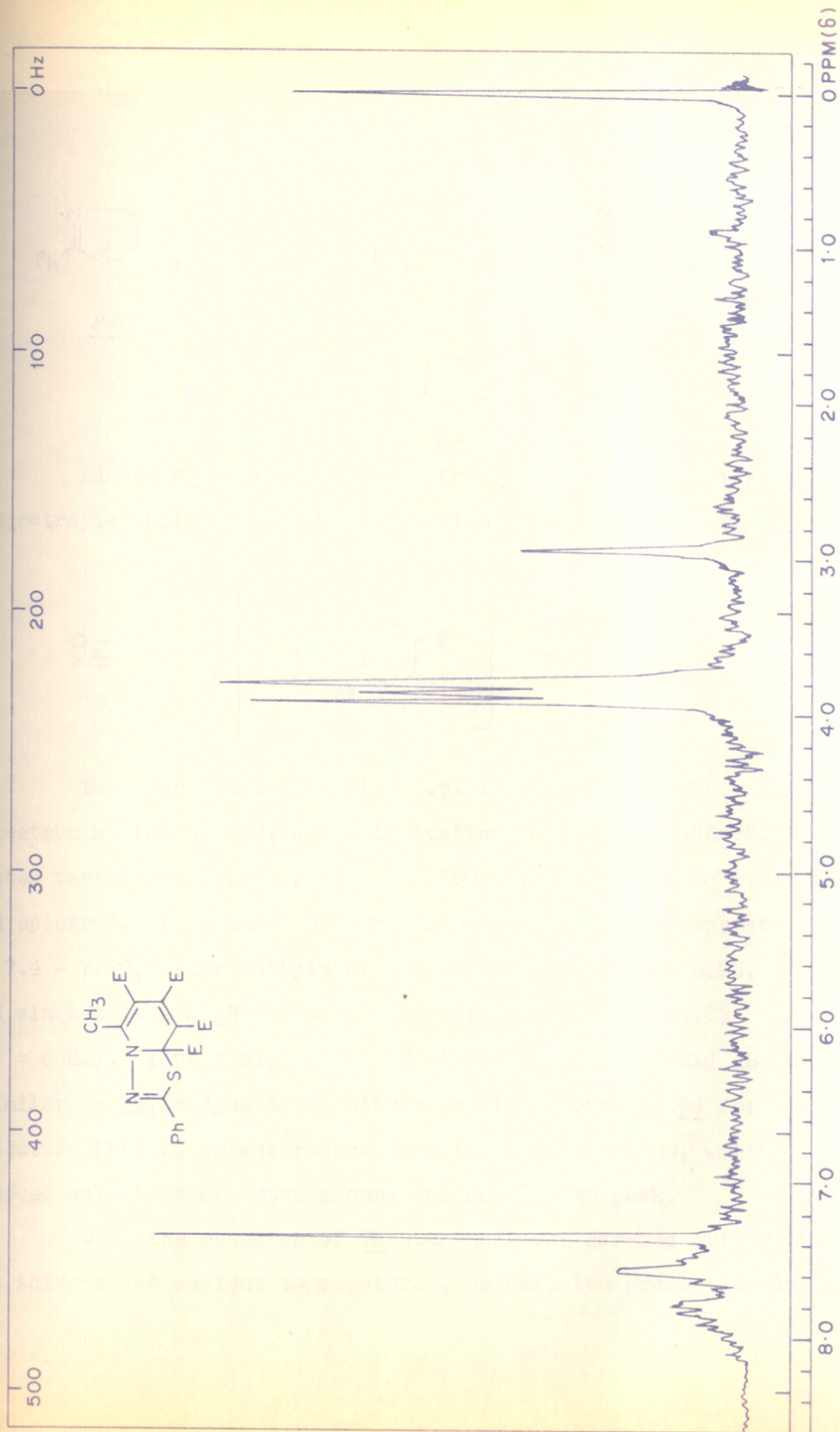


However, the major product of the reaction was a mixture of "red" adducts which could not be separated by chromatography or crystallization. The mass spectrum of this mixture indicated the presence of 1:3 molar adducts.

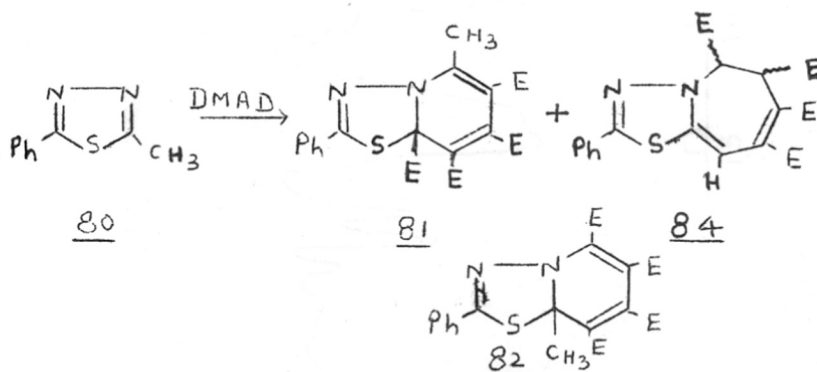


Under the same conditions, 2-methyl -5-phenyl-1,3,4-thiadiazole 80 (42) with DMAD gave a complex reaction mixture, which could be separated, by extensive chromatography, into a yellow adduct, m.p. 161° and an orange adduct, m.p. 171° .

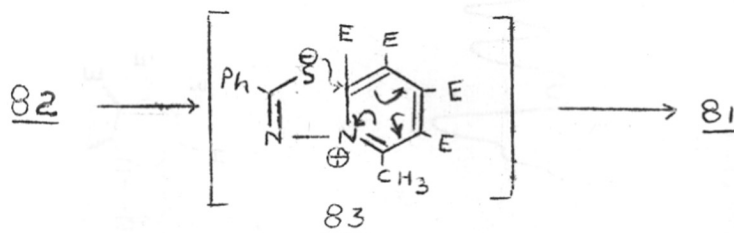
The yellow adduct, in the mass spectrum showed M^{+} ion at 460 indicating a 1:2 adduct. The IR spectrum showed ester carbonyl bands at 1685 and 1735 cm^{-1} . ^1H NMR spectrum consisted of aromatic signals at δ 7.4 - 8.0, ester methyls at δ 3.80, 3.86 and 3.96 and a 3H singlet at δ 3.0 for the methyl group. The chemical shift value of the methyl singlet at δ 3.0 demands the structure 81 for the yellow adduct and not the "labile" structure 82 as the latter would have been expected to exhibit the methyl singlet at ca. δ 1.4 (22,23).



^1H NMR OF COMPOUND 81

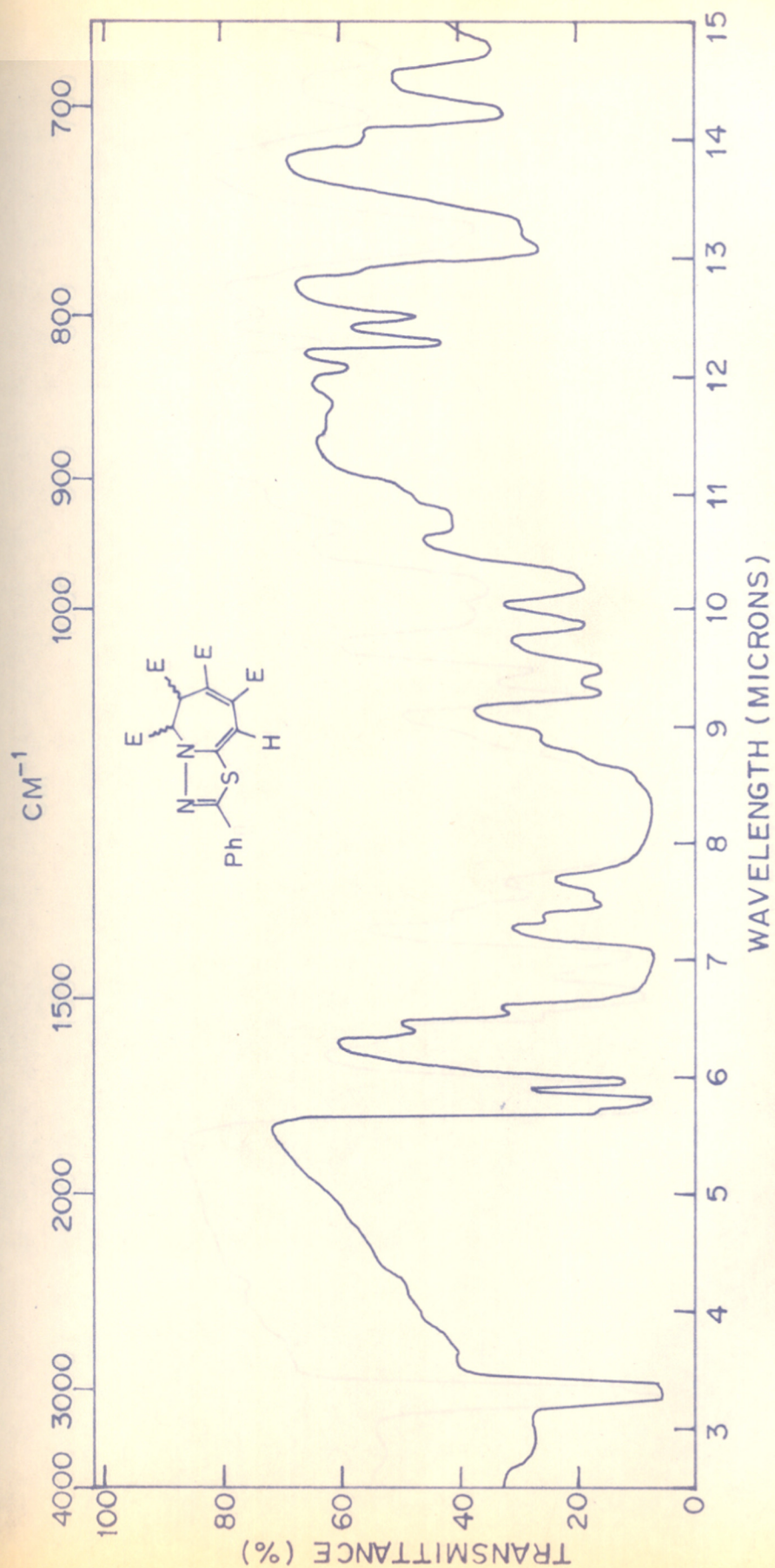


Adduct 81 could be formed from 82 by a 1,5 suprafacial sigmatropic shift or via the zwitterionic intermediate 83.

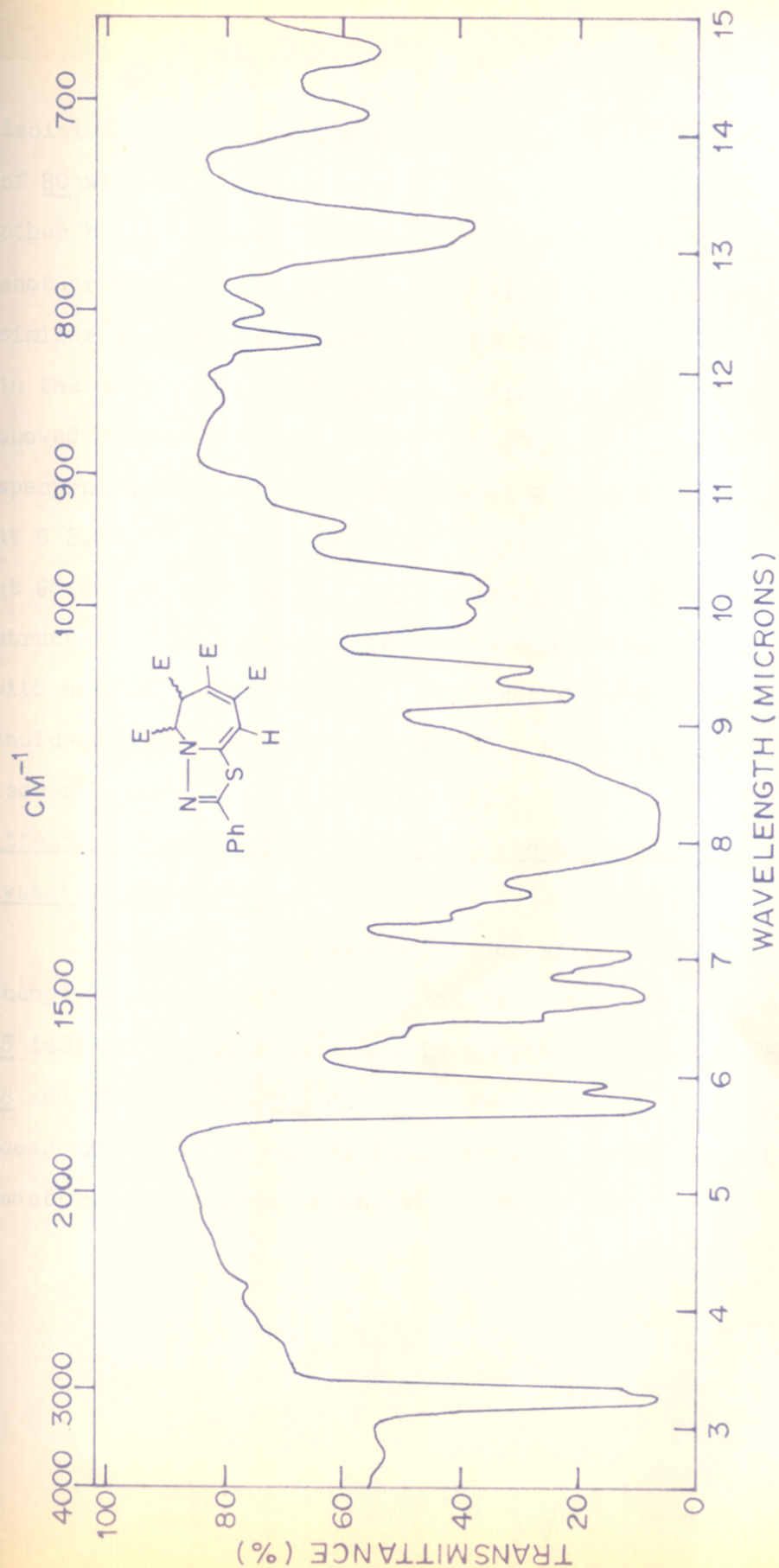


The orange adduct having m.p. 171° , showed in the mass spectrum M^{+} ion at 460, again indicating another 1:2 adduct. The ester carbonyl groups appeared at 1680, 1720 and 1750 cm^{-1} , in the IR spectrum. The ^1H NMR spectrum showed aromatic protons at δ 7.4 - 7.86, ester methyls at δ 3.70, 3.76, 3.83 and 3.90, a 1H singlet at δ 5.13 and an AB quartet at δ 5.43 and δ 6.13 ($J = 6\text{ Hz}$). Thus a high field 1H singlet with low field AB quartet, similar to 79, suggests the dihydroazepine structure 84 for this adduct. This is in accordance with its mass spectrum, which showed only loss of ester groups and no $M^{+} - 86$ peak.

When the reaction of 78 with DMAD was carried out in DMF as solvent at ambient temperatures, no definite product could be



IR OF COMPOUND 84: m.p. 171°

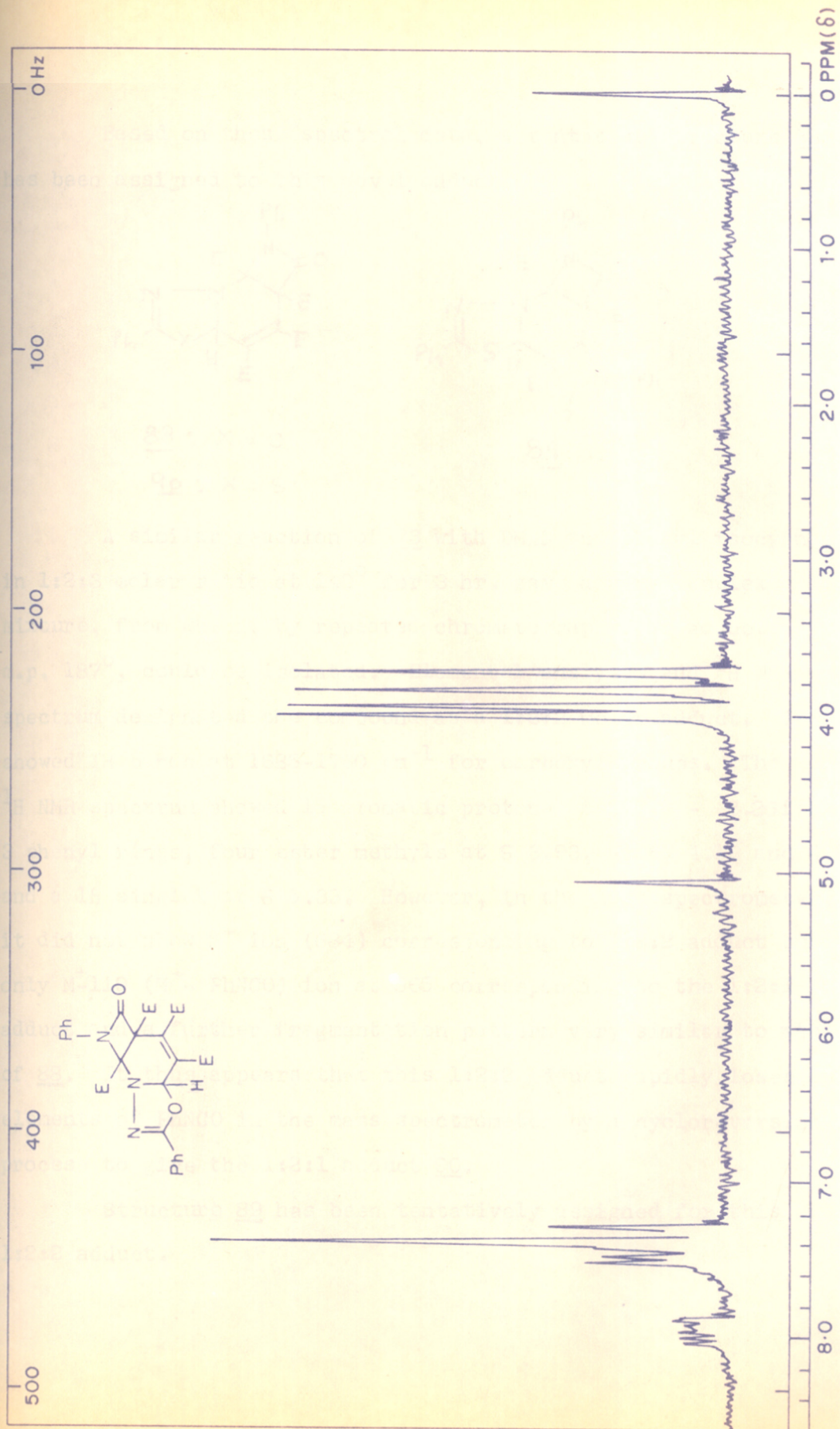


IR OF COMPOUND 84 : m.p. 72°

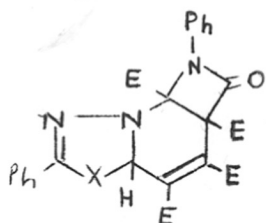
isolated from their highly complex reaction mixture. The reaction of 80 with DMAD in DMF at room temperature for 5 days, on the other hand, afforded by extensive chromatography, 81, 84 and another orange adduct, m.p. 72° . This compound had very similar spectral characteristics to those of 84. M^{+} ion at 460 in the mass spectrum indicated a 1:2 adduct. The IR spectrum showed ester carbonyls at 1690, 1730 and 1750 cm^{-1} . The ^1H NMR spectrum showed aromatic protons at δ 7.33 - 7.86, ester methylys at δ 3.66, 3.73 and 3.76, a 1H singlet at δ 5.03 and AB quartet at δ 5.30 and δ 6.03 ($J = 6\text{ Hz}$), inclining for the dihydroazepine structure. The mass spectrum also consisted only of ester losses with no $M-86$ peak. All this spectral data for this adduct indicates that it must have the same gross structure as 84 but isomeric with it (cis/trans).

Attempted reactions of phenyl isocyanate and phenyl isothiocyanate with 78 and 80

Both 78 and 80 did not react with phenyl isocyanate and phenyl isothiocyanate even at 140° for 8 hr. Compounds 85 (43) and 86 (44) were obtained from the reaction mixtures of 78 and 80 with ^{PhNCO}DMAD; 85 and 86 could be formed by hydrolytic decarboxylation of phenyl isocyanate to aniline and its further reaction with excess of phenyl isocyanate.

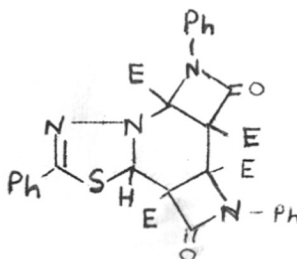


Based on these spectral data, a tentative structure 88 has been assigned to this novel adduct.



88 : X = O

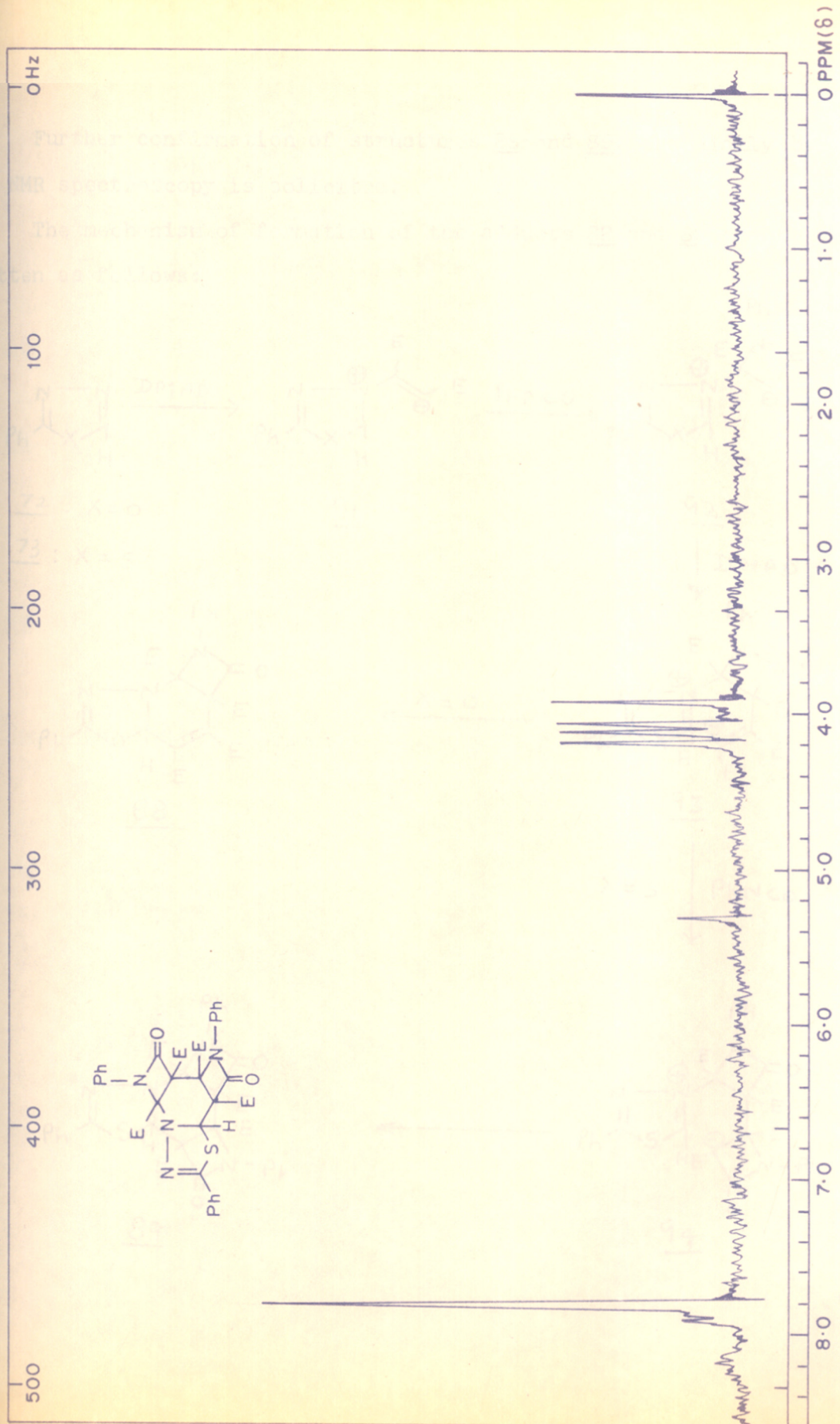
90 : X = S



89

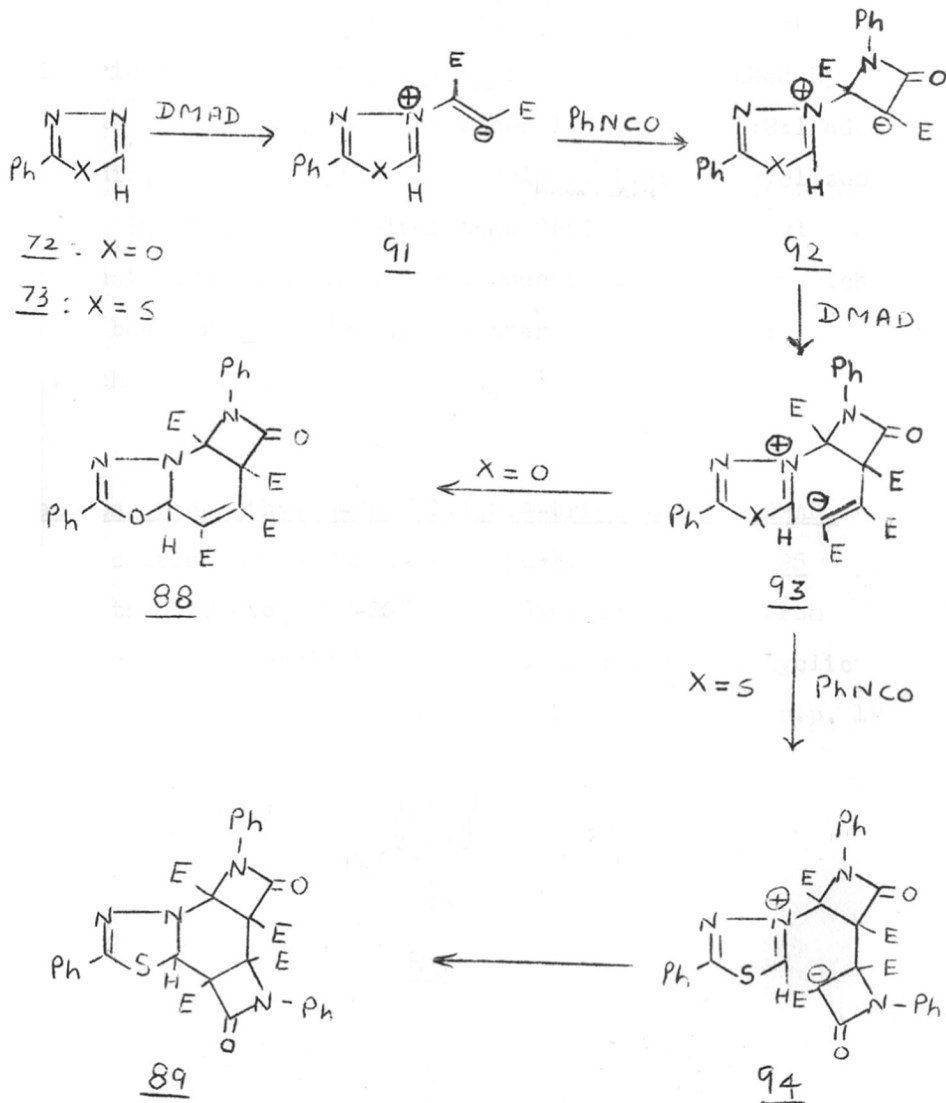
A similar reaction of 73 with DMAD and phenyl isocyanate in 1:2:3 molar ratio at 140° for 3 hr. gave a very complex mixture, from which, by repeated chromatography, an adduct, m.p. 187°, could be isolated. Elemental analyses and ¹H NMR spectrum designated the compound as a 1:2:2 molar adduct. It showed IR bands at 1685-1760 cm⁻¹ for carboxyl groups. The ¹H NMR spectrum showed 15 aromatic protons at δ 7.9 - 8.36 for 3 phenyl rings, four ester methyls at δ 3.93, 4.06, 4.13 and 4.20 and a 1H singlet at δ 5.33. However, in the mass spectrometer, it did not show M⁺ ion (684) corresponding to 1:2:2 adduct but only M⁺-119 (M⁺- PhNCO) ion at 565 corresponding to the 1:2:1 adduct and a further fragmentation pattern very similar to that of 88. It thus appears that this 1:2:2 adduct rapidly loses the elements of PhNCO in the mass spectrometer by a cycloreversion process to give the 1:2:1 adduct 90.

Structure 89 has been tentatively assigned for this 1:2:2 adduct.



Further confirmation of structures 88 and 89, especially by ^{13}C NMR spectroscopy is solicited.

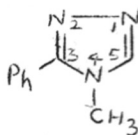
The mechanism of formation of the adducts 88 and 89 can be written as follows:



Phenyl isocyanate reacts in 2 +2 fashion with the electron rich double bond of the 1,4-dipole 91 formed by the initial reaction of DMAD with 72 or 73 to give the zwitterionic 1:1:1 adduct 92; 92 is further attacked by a molecule of DMAD to produce another 1:6 dipolar 1:2:1 adduct 93. This, in case of the oxadiazole derivative, cyclizes to 88. In case of the thiadiazole derivative, phenyl isocyanate cycloadds in a 2 + 2 mode to the electron rich double bond of 93 to produce another 1:6 dipolar 1:2:2 adduct 94 which finally cyclizes to 89.

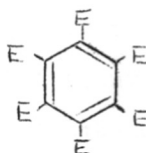
Reaction of 4-Methyl-3-Phenyl-1,2,4-triazole with DMAD

Reaction of 4-methyl-3-phenyl-1,2,4-triazole 95 (46) with DMAD even at -35° gave intractable tars from which no adducts could be isolated. However, the cyclic trimer of DMAD, mellitic acid hexamethyl ester 96, m.p. 186°



95

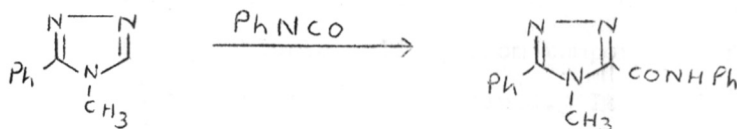
(47) was invariably formed in varying yields in this reaction.



96

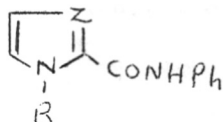
Reaction of 95 with phenyl isocyanate

Reaction of 95 with phenyl isocyanate either at 100° for 1 hr. or at room temperature for 10 hr. gave in 90% yield, a solid product, m.p. 220°. Its elemental analyses $\bar{C}$, H and $\bar{N}$ as well as M^+ ion at 278 in the mass spectrum identified the compound to be a 1:1 adduct. Its IR showed bands at 1600 and 1670 cm^{-1} . In analogy to the structure of 1:1 adducts of imidazoles 98 (48) and pyrroles 99 (49) with phenyl isocyanate, structure 97 has been tentatively assigned to it.



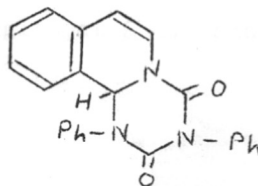
95

97



98 : Z = N

99 : Z = CH



100

Unfortunately, the ^1H NMR spectrum of 97 could not be taken due to its high insolubility in most of the solvents.

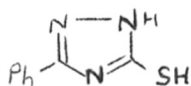
Significantly, no 1:2 molar adduct is formed in this reaction even with excess of phenyl isocyanate. Huisgen and coworkers (50) have isolated 1:2 molar adducts such as 100 from isoquinoline and phenyl isocyanate.

Reaction of 3-Mercapto-5-phenyl-1,2,4-triazole with DMAD

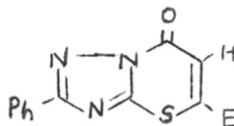
Recently Srinivasan and Upadhyaya (11) reported the reaction of 3-mercapto-5-phenyl-1,2,4-triazole 101 (51) with DMAD in refluxing methanol containing a trace of acetic acid to produce a 1:1 cycloadduct, m.p. 196° , to which structure 102 was proposed. It is reported to give M^+ ion at 287, IR bands at 1710 and 1750 cm^{-1} . Its ^1H NMR in TFA is reported to exhibit a 3H singlet at 6.85 for the ester methyl group, a 1H singlet for the olefinic proton at 6.6 and signals at 6.3 - 8.13 for 5 aromatic protons.

When this reaction was carried out in methanol containing few drops of hydrochloric acid at room temperature for 24 hours, a solid product, m.p. 197° was obtained. It gave M^+ ion at 287 indicating a 1:1 adduct with loss of elements of methanol. The IR spectrum showed carbonyl band at 1720 cm^{-1} . The ^1H NMR spectrum exhibited aromatic protons at 6.50 - 7.73 (3H) and 8.0 to 8.20 (2H), a 3H methyl singlet at 6.42 and a downfield

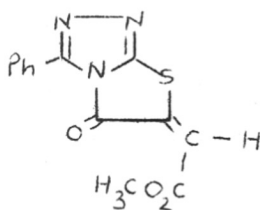
olefinic proton singlet at $\delta 7.90$.



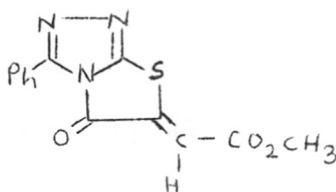
101



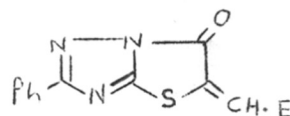
102



103a



103b



104

In analogy to the recent revision in the structures of addition products of DMAD with thiourea derivatives from dihydrothiazinone to thiazolinone structures (12), the DMAD adducts of 101 should also have the structures 103 or 104, considering 101 as a cyclic thiourea. Structures 103 look more probable as two ortho protons of the phenyl group appeared deshielded ($\delta 8.0 - 8.2$) in the ^1H NMR spectrum suggesting the presence of an electron withdrawing group adjacent to N_4 . The adduct, m.p. 196° (11), should be 103a, the cis-isomer, as the ester methyl is shielded ($\delta 3.85$) by the carbonyl group or the aromatic rings; the other adduct, m.p. 197° , exhibiting methyl singlet at $\delta 4.20$ should be 103b, the trans isomer. This needs further confirmation by ^{13}C NMR spectroscopy and X-ray crystallography.

1. Introduction

2. Objectives

3. Methodology

4. Results

5. Conclusion

6. References

7. Appendix

8. Notes

9. Index

10. Summary

11. EXPERIMENTAL

Preparation of diethyl hydrazino dioxalate 70

To a cooled solution (0°) of ethyl hydrazino oxalate 71 (45 g; 0.34 M) in 250 ml chloroform was slowly added with stirring ethyl oxalyl chloride (46.25 g; 0.34 M) maintaining the temperature below 5° throughout the addition. The reaction mixture was then stirred at $5-10^{\circ}$ for 2 hr. and room temperature for 1 hr. It was then filtered. The filtrate was concentrated and ether was added when needles of diethyl hydrazino dioxalate 70 separated out (26 g; 33%).

m.p.: 125° [Lit. $125-6^{\circ}$ (38)]

Preparation of 2,5-dicarbethoxy-1,3,4-oxadiazole 68

Compound 70 (22 g; 0.095 M) was taken in 150 ml xylene and to this 50 g phosphorus pentoxide and 50 g phosphorus oxychloride were added. The reaction mixture was then refluxed for 5 hr. After cooling, the liquid was decanted and the residual mass was extracted thrice with 50 ml hot xylene. All the xylene extracts were mixed and washed several times with 10% sodium bicarbonate solution and then with water. It was then dried and xylene was distilled under reduced pressure. The residue was chromatographed over silica gel (80 g) when 68 was obtained from pet. ether + benzene (1:1) fraction.

Yield: 10 g (49%). m.p. 54° .

Elemental analyses: Found, C: 44.62%; H: 4.50%; N: 13.33%.

$C_8H_{10}N_2O_5$ requires, C: 44.86%; H: 4.67%;
N: 13.08%.

IR ($\nu_{\max}^{\text{nujol}}$): 1745 (ester carbonyl).

¹H NMR (CCl₄): 1.53 (t, J = 7 Hz, 6H, methyl);
 4.5 (q, J = 7 Hz, 4H, methylene).
 M⁺ ion: 214.

Attempted reaction of 68 with DMAD

A mixture of 68 (0.214 g; 0.001 M) and DMAD (0.284 g; 0.002 M) was heated in an oil bath at 200° for 10 hr. under nitrogen atmosphere. Chromatography (silica gel, 1:20) of the mixture gave (0.265 g; 93%) DMAD (pet.ether) and the starting compound 68 (0.2 g; 93%) [benzene + pet.ether (1:1)]⁷.

Attempted reaction of 69 with DMAD

A mixture of 69 (0.444 g; 0.002 M) and DMAD (0.568 g; 0.004 M) was heated in an oil bath at 200° for 10 hr. under the atmosphere of nitrogen. The dark reaction mixture was then chromatographed over silica gel (1:15). Elution with pet.ether gave DMAD (0.54 g; 95%) while the starting compound 69 was obtained from pet.ether + chloroform (1:4) fraction (0.405 g; 91%).

Reaction of 2-phenyl-1,3,4-oxadiazole 72 with DMAD

A mixture of 72 (1.46 g; 0.01 M) and DMAD (2.84 g; 0.02 M) was heated in an oil bath at 160° for 3 hr. The dark coloured oil was then chromatographed over silica gel (1:20). Elution with pet.ether gave some unreacted DMAD (0.1 g; 3.5%) while from the benzene + chloroform (1:4) fraction the 1:2 adduct 74 was obtained as an oil (2.15 g; 50%). It was difficultly crystallized from benzene + pet.ether mixture or from ether into yellow needles (0.86 g; 20%) m.p.: 192°.

Compound 74

Elemental analyses: Found, C: 55.53%; H: 4.3%; N: 6.21%.

C₂₀H₁₈N₂O₉ requires, C: 55.81%; H: 4.18%;
 N: 6.51%.

IR (ν_{max} ^{nujol}): 1700 and 1745 (ester carbonyls); 1640 (C = N).

¹H NMR (CDCl₃): 3.80, 3.86 and 4.0 (three s, 12H, ester methyls);
6.2 (s, 1H, C₅-H); 7.33- 8.0 (m, 5H, aromatic).

Mass: 430 (M⁺ ion).

Reaction of 2-phenyl-1,3,4-thiadiazole 73 with DMAD

A mixture of 73 (1.62 g; 0.01 M) and DMAD (2.84 g; 0.02 M) was heated in an oil bath at 170° for 3 hr. The resulting tar was then chromatographed over silica gel (1:20). Elution with pet.ether gave some unreacted DMAD (0.14 g; 5%) while the 1:2 adduct 76 was obtained by the evaporation of the chloroform + benzene (1:3) fraction. The compound was crystallized from pet.ether + benzene (1.1 g; 25%) into a yellow orange solid, m.p. 196°.

Compound 76: Found, C: 53.88%; H: 3.81%; N: 5.98%.

C₂₀H₁₈N₂O₈S requires, C: 53.81%; H: 4.03%;
N: 6.28%.

IR (ν_{max} ^{nujol}): 1710, 1735 and 1750 (ester carbonyls).

¹H NMR (CDCl₃): 3.76, 3.86 and 3.96 (three s, 12H; methyl protons);
6.5 (s, 1H, C₅-H); 7.4 - 7.9 (m, 5H, aromatic).

Mass: 446 (M⁺ ion).

Attempted reaction of 72 and 73 with phenyl isocyanate and phenyl isothiocyanate

Compound 72 (0.146 g; 0.001 M) was heated with excess (5 ml) of phenyl isocyanate/isothiocyanate at 140° for 5 hr. under nitrogen atmosphere. TLC of the reaction mixture indicated no reaction. The reaction mixture was then passed through

silica gel column (1:15). Elution with pet.ether gave the unreacted phenyl isocyanate/isothiocyanate while the compound 72 came in chloroform + benzene (1:10) (0.13 g; 39%).

The reaction mixture obtained by heating 73 (0.162 g; 0.001 M) and excess (5 ml) of phenyl isocyanate/~~isothiocyanate~~ to 140° for 5 hr. also indicated no reaction (TLC). The reactants were separated by column chromatography (silica gel, 1:20; pet.ether and chloroform + benzene, 1:5); 0.15 g (92.5%) of 73 was recovered.

Reaction of 2-methyl-5-phenyl-1,3,4-oxadiazole 78 with DMAD

(a) Neat

A mixture of compound 78 (0.8 g; 0.005 M) and DMAD (1.42 g; 0.01 M) was heated on water bath for 4 hr. Initial colourless solution turned deep red after heating for 30 minutes. The reaction mixture, after 4 hr. of heating, was passed through a silica gel column (1:30). Elution with benzene gave unreacted DMAD (0.07 g; 5%). Benzene + 8% ethyl acetate fraction gave the 1:2 adduct 79 which was crystallized into yellow needles with ether (0.05 g; 2.25%). Evaporation of benzene + ethyl acetate (4:1) fraction gave the starting compound 78 (0.05 g; 6.25%) while a deep red coloured solid (0.4 g) was obtained by elution with benzene + ethyl acetate (1:1). However, the red solid was found to be a mixture (m.p. 50-80°) which could not be separated either by crystallization or by chromatography.

Compound 79: m.p. 134°.

Elemental analyses: Found, C: 56.92%; H:4.52%; N:6.47%.

$C_{21}H_{20}N_2O_9$ requires, C:56.75%; H:4.5%; N:6.31%.

IR (ν_{max} ^{nujol}): 1700, 1740, 1750 (ester carbonyls).

¹H NMR (CDCl₃): 3.66, 3.73, 3.80, 3.86 (four s, 12H, methyl protons); 4.9 (s, 1H, olefinic); 5.36 and 5.83 (AB quartet, J = 5 Hz; 2H, 2-protons on C₅-C₆); 7.3 - 8.1 (m, 5H, aromatic).

Mass: 444 (M⁺ ion).

(b) In DMF

The compound 78 (0.4 g; 0.0025 M) and DMAD (0.71 g; 0.005 M) were dissolved in DMF (5 ml) and kept at room temperature. The initial colourless solution became dark red after one month. TLC monitoring indicated a slow reaction producing a highly complex mixture of products. However, after evaporation of DMF under high vacuum followed by chromatography over silica gel, no definite product could be isolated in pure form from the resulting tar.

Reaction of 2-methyl-5-phenyl-1,3,4-thiadiazole 80 with DMAD

(a) Neat

A mixture of compound 80 (0.88 g; 0.005 M) and DMAD (1.42 g; 0.01M) was heated on a water bath for 3 hr. Originally colourless mixture turned reddish black after 3 hr. The highly complex reaction mixture (TLC) was then passed through a silica gel column (1:30). Elution was carried out with benzene + ethyl acetate (9:1) (500 ml). Evaporation of this fraction gave a yellowish orange mixture (0.5 g). This was rechromatographed over silica gel (1:20) with pet.ether + benzene (1:9) as eluent and 10 ml fractions were collected. Initial fractions gave the yellow compound 81 (0.15 g; 6.5%) while the latter fractions gave the orange 1:2 adduct 84 m.p. 171° (0.075 g; 3.25%).

Compound 81: m.p. 161° (ether + few drops of pet.ether).

Elemental analyses: Found, C: 54.92%; H: 4.34%; N: 5.96%.

$C_{21}H_{20}N_2O_8S$ requires, C: 54.78%;

H: 4.34%; N: 6.09%.

IR ($\nu_{\max}^{\text{nujol}}$): 1685, 1735 (carbonyl).

1H NMR ($CDCl_3$): 3.0 (s, 3H, methyl on Sp^2 carbon); 3.80, 3.86
3.96 (three s, 12H, ester methyls); 7.40 - 8.0
(m, 5H, aromatic).

Mass: 460 (M^+ ion).

Compound 84: m.p. 171° (ether).

Elemental analyses: Found, C: 54.61%; H: 4.19%; N: 6.13%.

$C_{21}H_{20}N_2O_8S$ requires, C: 54.78%; H: 4.34%;

N: 6.09%.

IR ($\nu_{\max}^{\text{nujol}}$): 1680, 1720, 1750 (ester carbonyl).

1H NMR ($CDCl_3$): 3.70, 3.76, 3.83, 3.9 (four s, 12H, ester
methyls); 5.13 (s, 1H, olefinic); 5.43 and 6.13
(AB quartet, $J = 6\text{Hz}$; 2H, 2 protons on C_5-C_6);
7.40 - 7.86 (m, 5H, aromatic).

Mass: 460 (M^+ ion).

(b) In DMF

Compound 80 (0.88 g; 0.005 M) and DMAD (1.42 g; 0.01M)
were mixed in about 5 ml of dry DMF and kept at room temperature.
After 5 days, the initial colourless solution turned dark red.
DMF was then distilled under high vacuum. The residue was
dissolved in ethyl acetate, washed with water, dried (Na_2SO_4)

and ethyl acetate distilled under vacuum. The residual complex was then chromatographed over silica gel (1:30). Elution with pet.ether + benzene (19:1) gave DMAD (0.04 g; 3%) while the unreacted starting compound 80 (0.045 g; 5%) was obtained from benzene fraction. A 500 ml fraction of ethyl acetate + benzene (1:9) was then collected; evaporation of this fraction gave 0.4 g of a mixture. This mixture was rechromatographed over silica gel (1:20). Elution was carried out with benzene + 1% ethyl acetate with 10 ml fractions collection. The initial fractions gave the yellow compound 81 (15 mg; 0.65%), followed by the orange compound 84 m.p. 72° (0.275 g; 12%) from the intermediate lot of fractions. Another orange compound 84, m.p. 171° was obtained from the last part of the fractions. Compound 81 : m.p. 161° .

This had superimposable IR and undepressed mixed m.p. with the compound 81 obtained from the next fraction (a).

Compound 84 : m.p.: 72° (benzene + pet.ether).

Elemental analyses: Found, C: 54.70%; H: 4.31%; N: 6.2%.

$C_{21}H_{20}N_2O_8S$ requires, C: 54.78%; H: 4.34%;

N: 6.09%.

IR (ν_{max} nujol) : 1690, 1730, 1750 (ester carbonyls).

1H NMR ($CDCl_3$): 3.66, 3.73 and 3.76 (three s, 12H, methoxy protons);

5.03 (s, 1H, olefinic proton); 5.30 and 6.03 (AB quartet, $J = 6$ Hz; 2H, 2 protons on C_5-C_6);

7.33 - 7.86 (m, 5H, aromatic).

Mass : 460 (M^+ ion).

Compound 84: m.p. 171° .

This compound had superimposable IR and undepressed mixed m.p. with the compound 84, m.p. 171° , obtained from the neat reaction (a).

Attempted reaction of 78 and 80 with phenyl isocyanate and phenyl isothiocyanate

A mixture of compound 78/80 and excess of phenyl isocyanate/isothiocyanate was heated at 140° for 8 hr. in an atmosphere of nitrogen. Then the unreacted isocyanate/isothiocyanate was removed under high vacuum. The residue was then chromatographed over silica gel (1:20). Elution with benzene gave the starting compound 78/80. Compound 85 was obtained in variable yields from the benzene + ethyl acetate (9:1) fraction while the compound 86 was obtained by elution with ethyl acetate + benzene (3:7) mixture in poor yields.

Compound 85: m.p.: 238° [Lit. $238-9^{\circ}$ (43)].

Compound 86: m.p.: 150° [Lit. $150-51^{\circ}$ (44)].

Reaction of 72 with DMAD + phenyl isocyanate

A mixture of the compound 72 (1.46 g; 0.01 M), DMAD (2.84 g; 0.02 M) and phenyl isocyanate (3.57 g; 0.03 M) was heated in an oil bath at 140° for 3 hr. The crude reaction mixture was then passed through silica gel column (1:15). Elution with pet. ether gave a mixture (0.5g) of unreacted DMAD and phenyl isocyanate while elution with chloroform + benzene (1:4) gave the white compound 88 (2.75 g; 50%).

Compound 88: m.p. 208° (pet. ether + benzene, 1:4)

Elemental analyses: Found, C: 59.4%; H: 4.16%; N: 7.33%.

$C_{27}H_{23}N_3O_{10}$ requires, C: 59.02%; H: 4.18%;
N: 7.65%.

IR($\nu_{\max}^{\text{nujol}}$): 1690-1770 (b, carbonyl groups).

$^1\text{H NMR}$ (CDCl_3): 3.76, 3.86, 3.96, 4.03 (four s, 12H, methyl groups); 5.1 (s, 1H, bridgehead proton);
7.36 - 7.56 and 7.86 - 8.10 (m, 10H, aromatic).

Mass : 549 $[\text{M}^+ \text{ion}]$.

Reaction of 73 with DMAD + phenyl isocyanate

A mixture of the compound 73 (1.62 g; 0.01M), DMAD (2.84 g; 0.02 M) and phenyl isocyanate (3.57 g; 0.03 M) was heated in an oil bath at 140° for 3 hr. A dark coloured liquid thus obtained was passed through a silica gel column (1:10). Elution with pet. ether + benzene (3:1) gave the compound 85 (0.25 g) while from pet. ether + benzene (1:1) fractions compound 89 (0.48 g; 7%) was obtained. It was crystallized difficultly from ether into pale yellow needles (0.15 g; 2.2%).

Compound 89: m.p. 187° .

Elemental analyses: Found, C: 59.56%; H: 3.98%; N: 8.41%.

$C_{34}H_{28}N_4O_{10}S$ requires, C: 59.65%;
H: 4.09%; N: 8.18%.

IR($\nu_{\max}^{\text{nujol}}$) : 1685 - 1760 (b, carbonyl groups).

$^1\text{H NMR}$ (CCl_4): 3.93, 4.06, 4.13, 4.2 (four s, 12H, methyl protons);
5.33 (s, 1H, bridgehead proton); 7.9 - 8.36
(m, 15H, aromatic).

Mass: 565 $[\text{M}^+ - 119]$

Reaction of 4-methyl-3-phenyl-1,2,4-triazole 95 with DMAD

To a cooled solution of 95 (0.159 g; 0.001 M) in chloroform (5 ml) at -35° was added slowly DMAD (0.284 g; 0.002 M) in chloroform (5 ml) during 4 hr. maintaining the temperature below -30° . After removal of chloroform under reduced pressure, the resulting tar was chromatographed over silica gel (1:30). Elution with benzene gave mellitic acid hexamethyl ester 96 (0.05 g).

Compound 96: m.p. 186° [Lit. 188° (47)].

No other compound could be obtained in a pure state from the other fractions or by rechromatography.

Reaction of 95 with phenyl isocyanate

A mixture of compound 95 (1.59 g; 0.01M) and phenyl isocyanate (1.19 g; 0.01M) was either kept at room temperature for 10 hr. or heated at 100° for 1 hr. The reaction mixture then solidified. The solid compound 99 was filtered and washed with benzene (2.5 g; 90%). $\alpha\eta$

Compound 99: m.p. 220° .

Elemental analyses: Found, C: 69.32%; H: 4.94%; N: 20.19%.

$C_{16}H_{14}N_4O$ requires, C: 69.06%; H: 5.03%;
N: 20.14%.

IR(ν_{max} , ν_{Nujol}): 1670 (carbonyl); 1600 (aromatic).

Mass: 278 [M^{+} ion]

Reaction of 3-mercapto-5-phenyl-1,2,4-triazole 101 with DMAD

Compound 101 (0.354 g; 0.002 M) and DMAD (0.284 g; 0.002 M) were dissolved in methanol (15 ml) containing 3-4 drops of dil. hydrochloric acid. The solution was allowed to stand at room temperature for 24 hr. Methanol was then evaporated off. The residue was crystallized from benzene to colourless crystals of 103b (0.21 g; 36.5%).

Compound 103b: m.p. 197°.

Elemental analyses: Found C: 54.11%; H: 3.18%; N: 14.5%.

$C_{13}H_9N_3O_3S$ requires, C: 54.35%; H: 3.13%;
N: 14.63%.

IR ($\nu_{\max}^{\text{nujol}}$): 1720 (carbonyl).

1H NMR (TFA): 4.2 (s, 3H, methyl protons); 7.9 (s, 1H, olefinic);
7.5 - 7.73 (m, 3H, m and p aromatic protons)
8.0 - 8.2 (m, 2H, -o aromatic protons).

Mass: 287 $[M^+ \text{ ion}]$.

*R.B. Mitra, G.H. Kulkarni, G.S. Shirwaiker and R.S. Jagtap in R.M. Acheson, R.B. Mitra, N.R. Ayyangar and V.N. Gogte (Ed.), New Trends in Heterocyclic Chemistry, (Elsevier), (in press).

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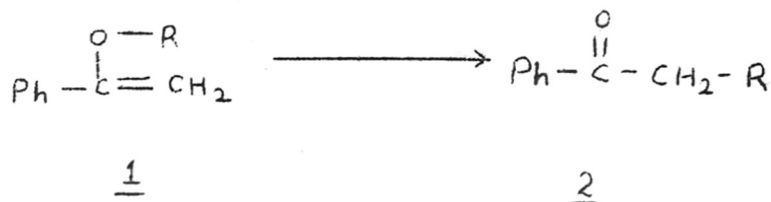
CHAPTER II

THERMAL REARRANGEMENT REACTIONS OF SOME ALKYLTHIO SUBSTITUTED TRIHETEROATOMIC AZOLES

A BRIEF INTRODUCTION TO

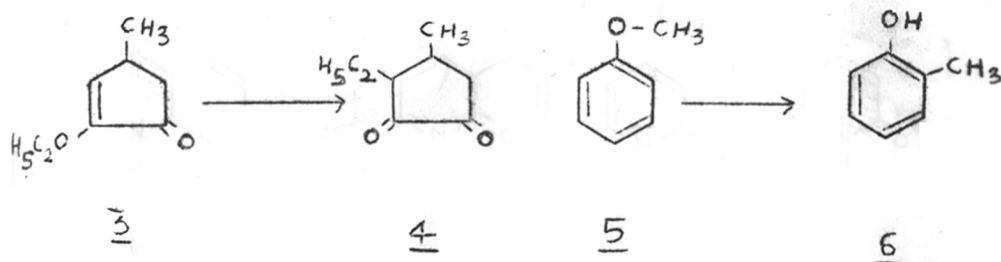
1,3 ALKYL MIGRATIONS

As early as in 1896, Claisen (1) observed the thermal rearrangement of α -alkoxystyrenes 1 to the corresponding substituted acetophenones 2.



Since then, the 1,3-alkyl migration reactions have been extensively studied with a broad spectrum of organic compounds including alicyclic, carboxylic as well as heterocyclic systems.

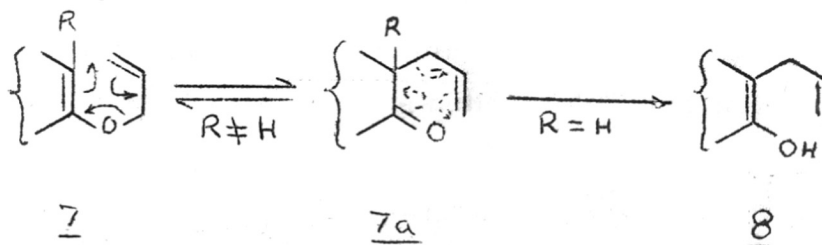
The 1,3 C $\rightarrow$ O alkyl migrations in many enol ethers like 2-ethoxy-4-methylcyclopent-2-eneone 3 to 3-ethyl-4-methyl-1,2-cyclopentanedione 4 (2), anisole 5 to 2-methyl phenol 6 (3) etc. have been very well established.



These reactions are known to proceed through an intramolecular free radical pathway.

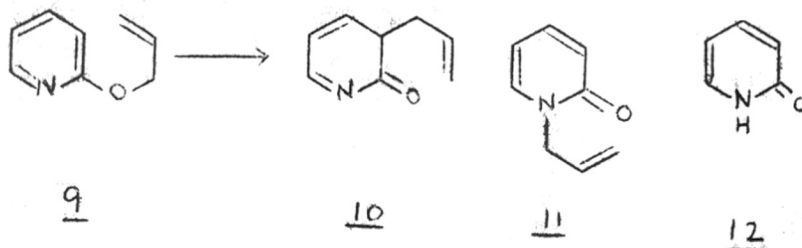
The thermal Claisen rearrangement of allyl aryl ethers 7 to o-allyl phenols 8 have been studied in vast detail. This rearrangement is proved to be an intramolecular, suprafacial-

suprafacial, aromatic $[3,3]$ sigmatropic process, the cyclic, 6-membered activated complex of which has little polar character (4,5).



When $R \neq H$ in 7, a retero-Claisen rearrangement of 7a can also take place to give back 7.

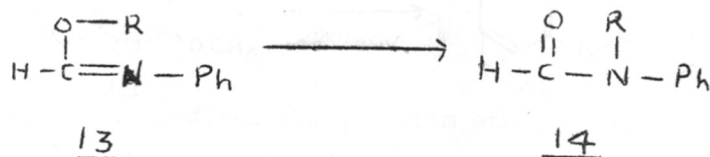
A large number of heterocyclic systems are also known to undergo Claisen rearrangement e.g. 2-allyloxypyridine 9 rearranges into 3-allyl-2-pyridone 10, 1-allyl-2-pyridone 11, and 2-pyridone 12 (6).



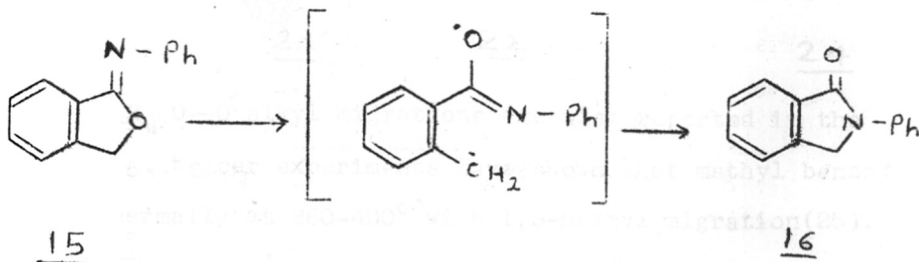
Similar Claisen rearrangements with $1,3 O \rightarrow N$ or $O \rightarrow C$ allyl migrations have been studied for quinolines (7), pyrimidines (8), benzimidazoles (9), triazolopyrimidines (10), purines (11), etc.

The thio-Claisen rearrangement reactions proceeding with 1,3 S $\rightarrow$ C allyl migrations are also known for a variety of allylthio ethers with carbocyclic and heterocyclic systems (12,13).

The thermal rearrangement reactions of alkyl imidates 13 to amides 14 by a 1,3 O $\rightarrow$ N alkyl migration are also known (14,15); however they seem to be limited to methyl and benzyl derivatives.

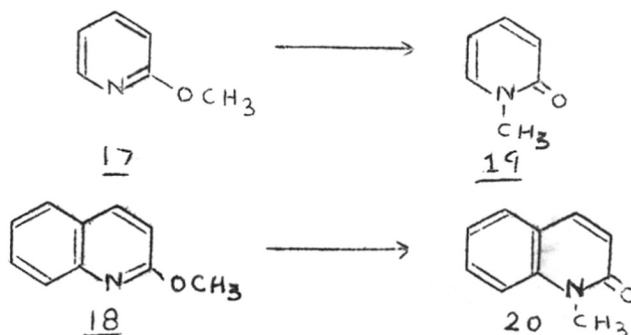


These reactions are catalysed by alkyl halides or alkyl sulfates (16,17). These rearrangements are proved to be intermolecular by intercepting the rearranging intermediate and incorporating a new, more stable alkyl group into the molecule (18). This rearrangement also occurs in cyclic systems e.g. the cyclic benzyl imidate 15 undergoes C-O bond fission at 300° with recyclisation in 1,3 manner to produce the isoindole derivative 16.



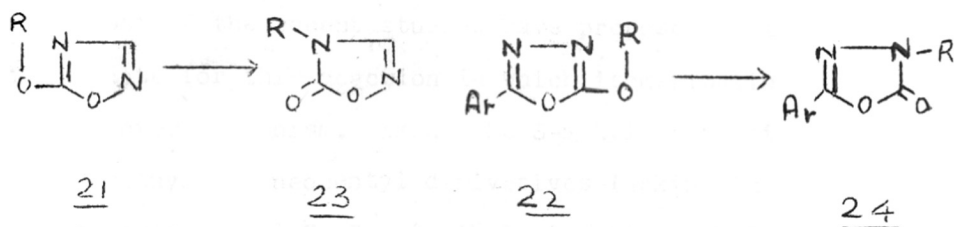
This 1,3 O $\rightarrow$ N alkyl migration reaction is well introduced in many heterocyclic systems. Thus 2-methoxy-

pyridines 17 and quinolines 18 thermally rearrange into the corresponding N-methyl-pyridones 19 and quinolones 20 (19).

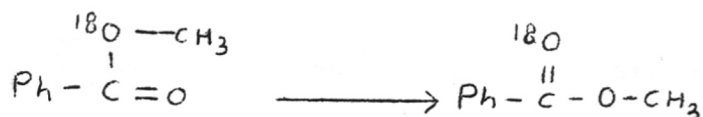


Alkoxyimidines (20), lactim ethers (21), quinazoline ethers (22) etc, also undergo related 1,3 alkyl migrations.

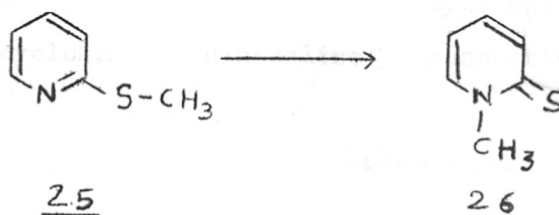
5-Alkoxy-1,2,4-oxadiazoles 21 as well as 2-alkoxy-5-aryl-1,3,4-oxadiazoles 22 thermally undergo such 1,3 alkyl migrations and form 4-alkyl-1,2,4-oxadiazol-5(4H)-ones 23 and 3-alkyl-5-aryl-1,3,4-oxadiazol-2(3H)-ones 24 (24) respectively.



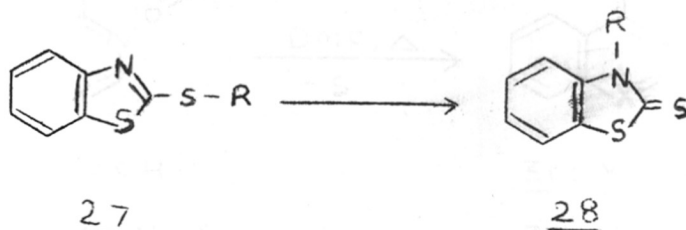
The 1,3 O $\rightarrow$ O alkyl migrations are also reported in the literature e.g. tracer experiments have shown that methyl benzoate rearranges thermally at 360-400° with 1,3-methyl migration(25).



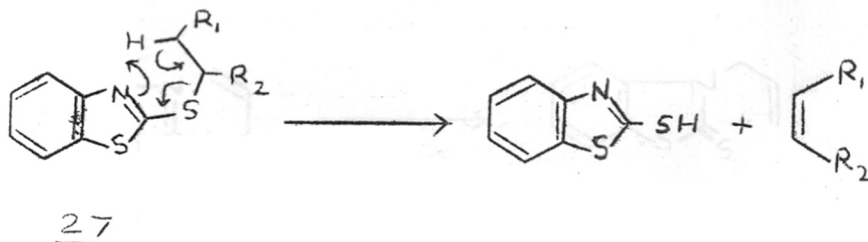
2-Methylthio-pyridine 25 rearranges thermally to N-methyl-2-pyridithione 26 by a 1,3 S $\rightarrow$ N methyl migration; but this reaction is more sluggish than with the oxygen analog (26).



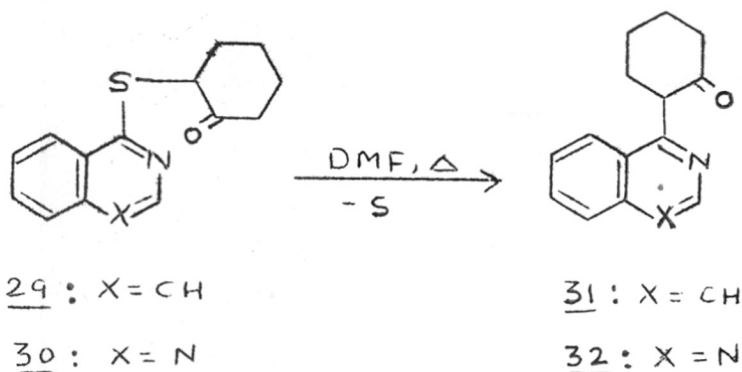
2-Alkylthio-benzothiazoles 27 are reported to thermally isomerize to 3-alkyl-benzothiazolin-2-thiones 28 (27-30).



Most of the recent studies have proposed an ion pair intermediate for this reaction in which isomerization occurs by a 4-center mechanism. Among the S-alkyl derivatives of 27, benzyl, methyl and neopentyl derivatives lacking in β -hydrogen atoms undergo such 1,3 S $\rightarrow$ N alkyl migrations while 27 with alkyl groups containing a β -hydrogen atom yield olefines along with 2-mercapto-benzothiazole by pyrrolitic elimination.

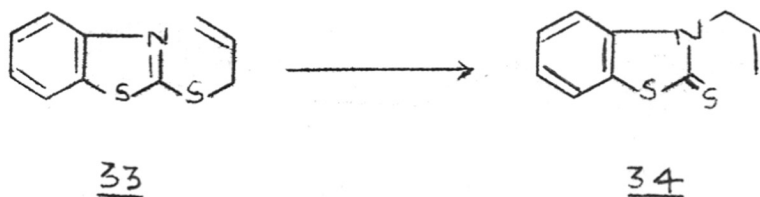


However, Harjit Singh et al. reported that when 1-[(α -oxocyclohexyl)thio]-isoquinoline 29 and 4-[(α -oxocyclohexyl)thio]-quinazoline 30 are thermolysed in Dimethylformamide (DMF), instead of 1,3 S $\rightarrow$ N migrations mentioned above, they extrude elemental sulfur and form 1-(α -oxocyclohexyl)-isoquinoline 31 and 4-(α -oxocyclohexyl)-quinazoline 32 respectively (31).

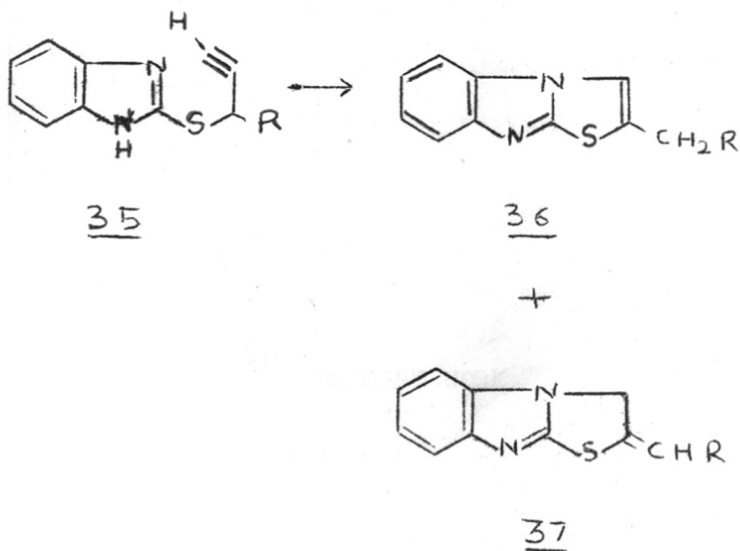


However the corresponding cyclohexenylthio derivatives of isoquinoline and quinazoline are found to be stable.

Recently Takeo et al. (32) have observed that thio-Claisen rearrangement of 2-allylthio-benzothiazole 33 which rearranges to N-allyl-benzothiazol-2(3H)-thione 34 by 1,3 S $\rightarrow$ N allyl migration.

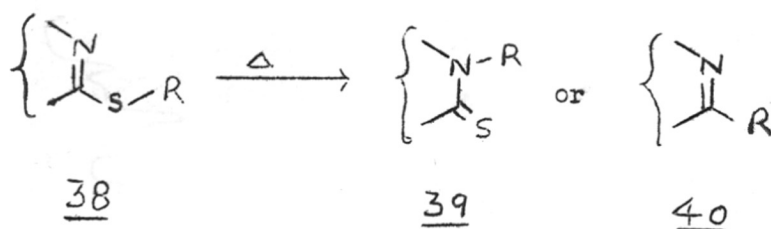


A similar rearrangement with 1,3 S $\rightarrow$ N migration is also known in benzimidazole 35; however the product further rearranges to 36 and 37 (33).

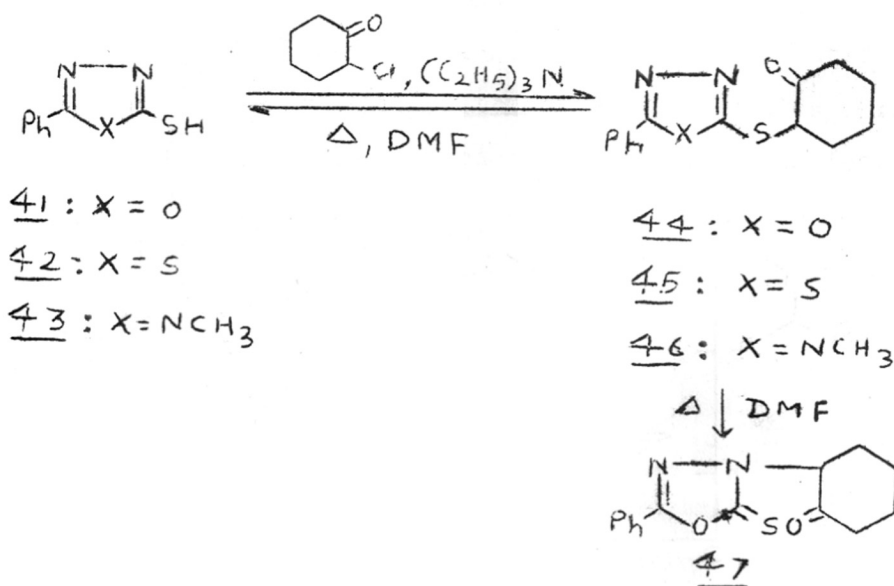


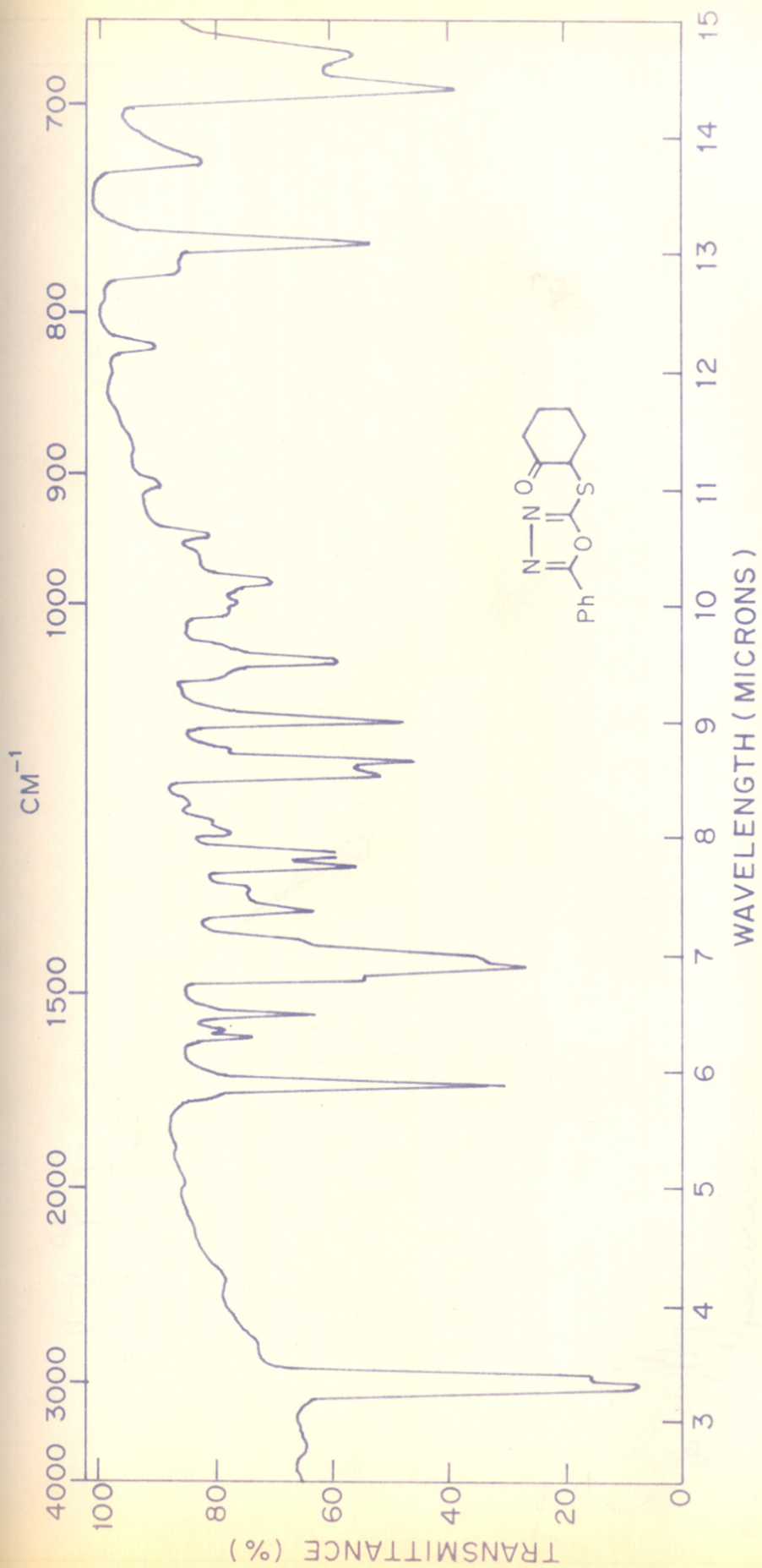
PRESENT WORK

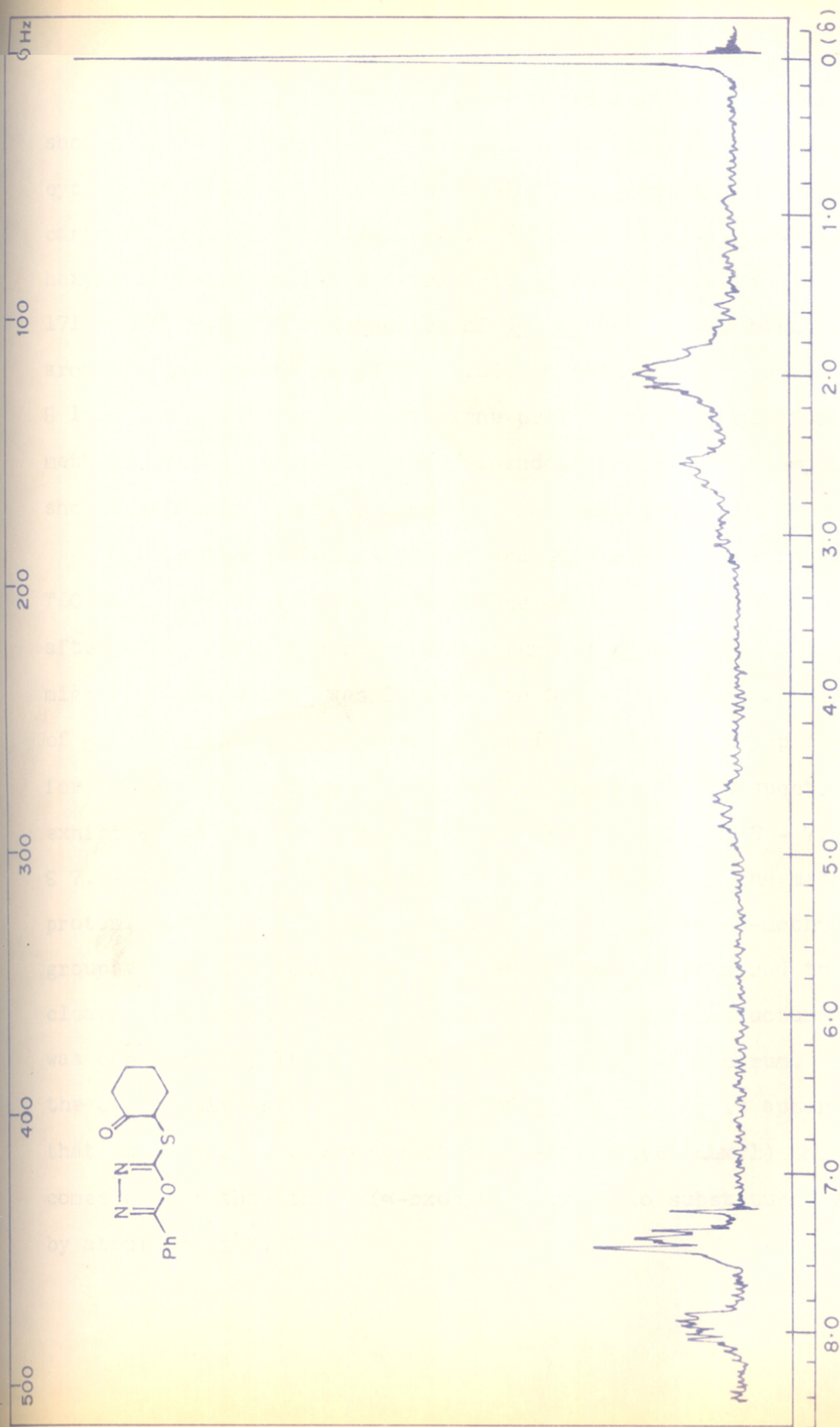
As the imino-alkylthioethers 38 at high temperatures are known either to rearrange by 1,3 S $\rightarrow$ N alkyl migration to form N-alkyl thiones 39 or to extrude elemental sulfur to produce the corresponding imino-alkyl derivatives 40, it was interesting to see the behaviour of alkylthio substituted derivatives of some symmetrical triheteroatomic azoles viz. 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles.



The (α -oxocyclohexyl)thio substituted triheteroatomic azoles 44, 45, 46 were prepared by condensation of the corresponding thiols 41 (34), 42 (35), 43 (36) with α -chloro-cyclohexanone in refluxing benzene containing equimolar amounts of triethylamine.

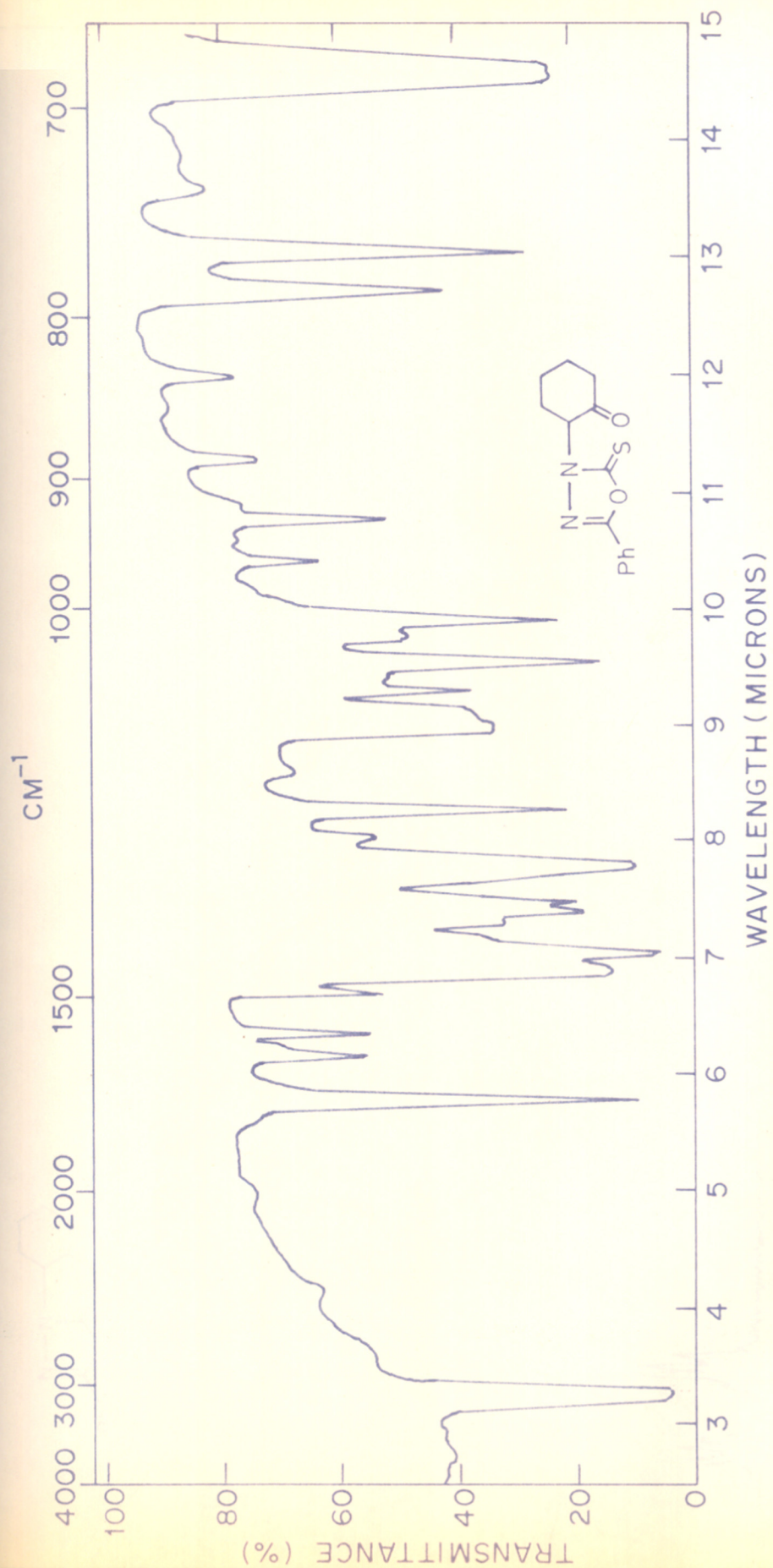


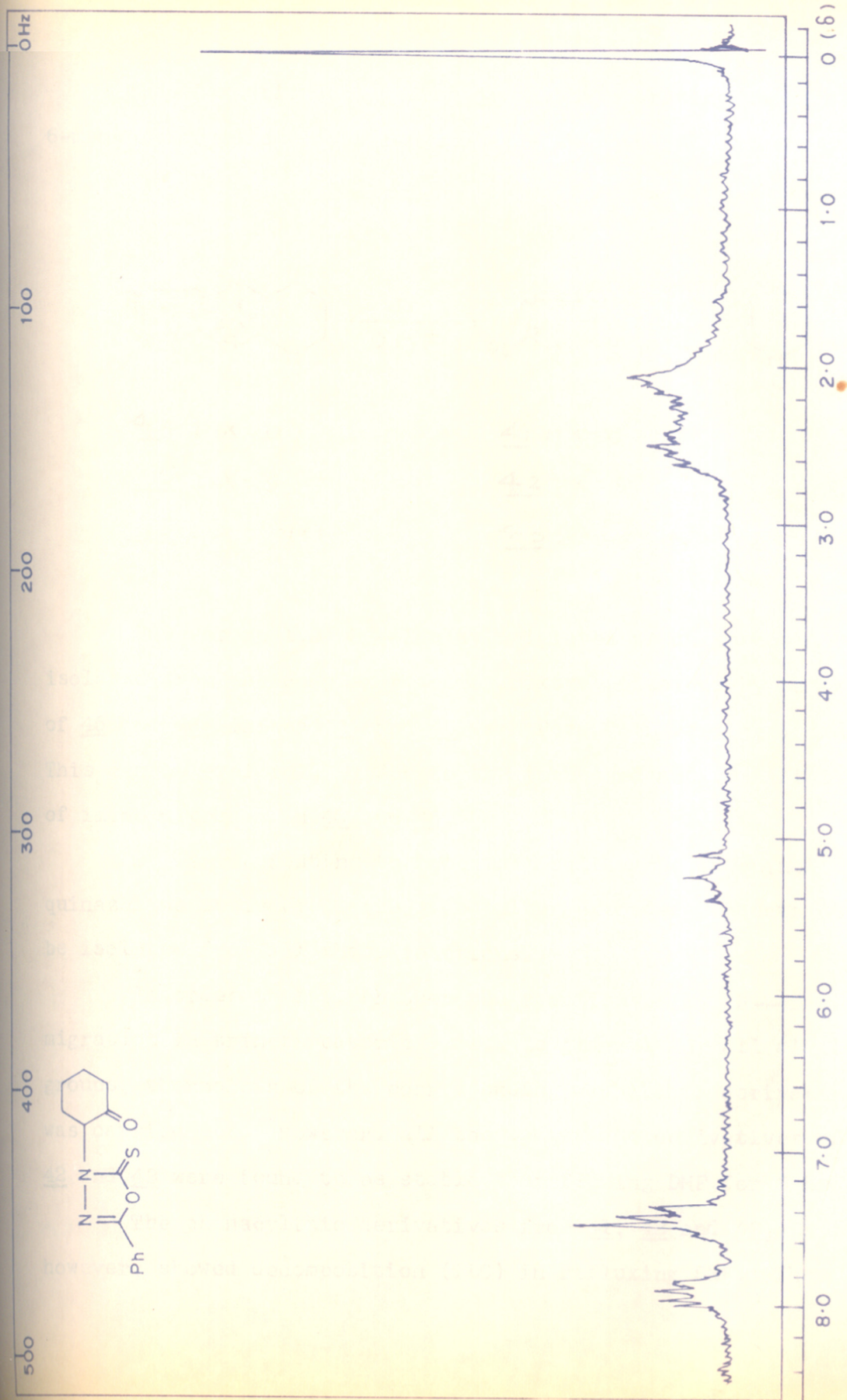




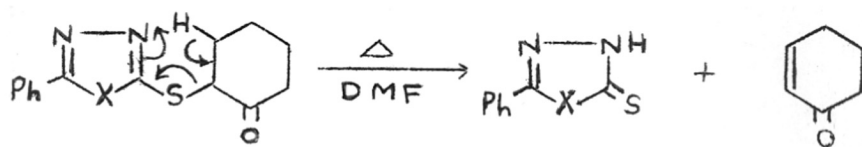
2-[α -Oxocyclohexyl]thio-5-phenyl-1,3,4-oxadiazole 44 showed IR band at 1710 cm^{-1} for the carbonyl group; 2-[α -oxocyclohexyl]thio-5-phenyl-1,3,4-thiadiazole 45 showed the carbonyl frequency at 1705 cm^{-1} . While 4-methyl-5-[α -oxocyclohexyl]thio-3-phenyl-1,2,4-triazole 46 gave the IR band at 1715 cm^{-1} . The ^1H NMR spectra of 44, 45 and 46 exhibited aromatic multiplets at $\delta 7.2 - 8.06$, 8H multiplets between $\delta 1.55$ and $\delta 3.2$ for the methylene protons and signals for the methine proton at $\delta 4.50 - 5.0$; in addition to this, compound 46 showed a 3H singlet at $\delta 3.63$ for the N-CH_3 group.

When the compounds 44, 45 and 46 were refluxed in DMF, ✓
 TLC indicated complete disappearance of the starting materials after 3 hr. From the reaction mixture of 44 the 1,3 S $\rightarrow$ N migration product 47 was isolated in 30% yield along with 15% ✓
 of 41. The thione 47 showed in its IR spectrum a sharp peak for the carbonyl group at 1735 cm^{-1} . In the ^1H NMR spectrum, it exhibited multiplets for 5 aromatic protons at $\delta 7.33 - 7.50$ and $\delta 7.80 - 8.0$, a 1H ABX signals at $\delta 5.1 - 5.55$ for the methine proton, and 8H multiplets at $\delta 1.90 - 2.80$ for the 4-methylene groups. The deshielding of the methine proton compared to 39 clearly indicated the 1,3 S $\rightarrow$ N migration. This structure was confirmed by its M^+ ion at 274 in the mass spectrum. From the comparative study of the IRs of 44 and 47, it is apparent that the carbonyl frequency of the N-(α -oxocyclohexyl) thione comes higher than the (α -oxocyclohexyl)thio substituted azole by about 25 cm^{-1} .



^1H NMR OF COMPOUND 47

The formation of 41 from 44 may be operating through a 6-membered cyclic transition state as shown. ✓



44 : X = O

41 : X = O

45 : X = S

42 : X = S

46 : X = NCH₃

43 : X = NCH₃

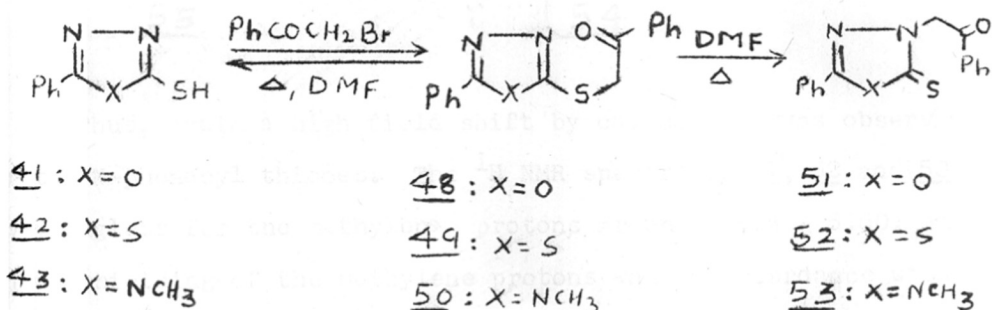
However no 1,3 S $\rightarrow$ N alkyl migrated products could be isolated from the complex reaction mixture obtained by thermolysis of 45 and 46; instead 42 and 43 were formed in varying yields. ✓ This can be explained as due to the increased nucleophilicity of imino nitrogen in 45 and 46.

It is interesting to note that unlike the isoquinoline and quinazoline derivatives (29), no sulfur extruded products could be isolated from all these reactions.

In order to see, whether the reaction of 1,3 S $\rightarrow$ N alkyl migration in triheteroatomic azoles is general for all alkyl groups, thermolysis of the corresponding methylthio derivatives was carried out. However, all the methylthio derivatives of 41, 42 and 43 were found to be stable to refluxing DMF for 3 hr.

The phenacylthio derivatives from 41, 42 and 43, however, showed decomposition (TLC) in refluxing DMF. The

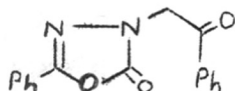
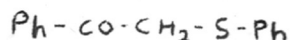
phenacylthio substituted azoles 48, 49 and 50 were prepared by the condensation of equimolar amounts of the thiols 41, 42 and 43 respectively with phenacyl bromide either in refluxing benzene containing triethylamine for 2 hr. or in DMF at room temperature for 24 hr.



The compounds 48, 49 and 50 in their IR spectra, showed a sharp peak at 1670 cm⁻¹ for the carbonyl group, in analogy to phenacyl thiophenol 54 which absorbs at 1660 cm⁻¹. In their ¹H NMR spectra the singlet for the methylene protons attached to sulfur appeared around 64.9 - 5.0.

When the compounds 48, 49 and 50 were refluxed in DMF for 3 hr. the 1,3 S → N phenacyl migrated products 51, 52 and 53 respectively were obtained in poor yields along with the major products 41, 42 and 43.

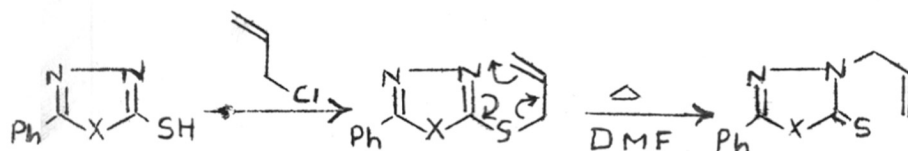
The compounds 51, 52 and 53, in their IR spectra showed a sharp peak at 1700 cm^{-1} for the carbonyl group similar to the phenacyl carbonyl absorption of 55 at 1700 cm^{-1} .

5554

Thus, again a high field shift by ca. 30 cm^{-1} was observed for the N-phenacyl thiones. The ^1H NMR spectra of 51, 52 and 53 gave singlets for the methylene protons around $\delta\ 5.4 - 5.50$. This deshielding of the methylene protons was in accordance with the N-phenacyl structures assigned to them.

The tendency of the triheteroatomic azoles mentioned above, to abstract a β -hydrogen atom to form the respective thiones revealed that such heteroatomic systems with thioallyl substituents may also undergo the thio-Claisen rearrangement reaction which necessarily proceeds through an intramolecular 6-membered cyclic transition state.

The thioallyl azoles 56, 57 and 58 were prepared by condensation of 41, 42 and 43 respectively with allyl chloride in refluxing benzene containing triethylamine.

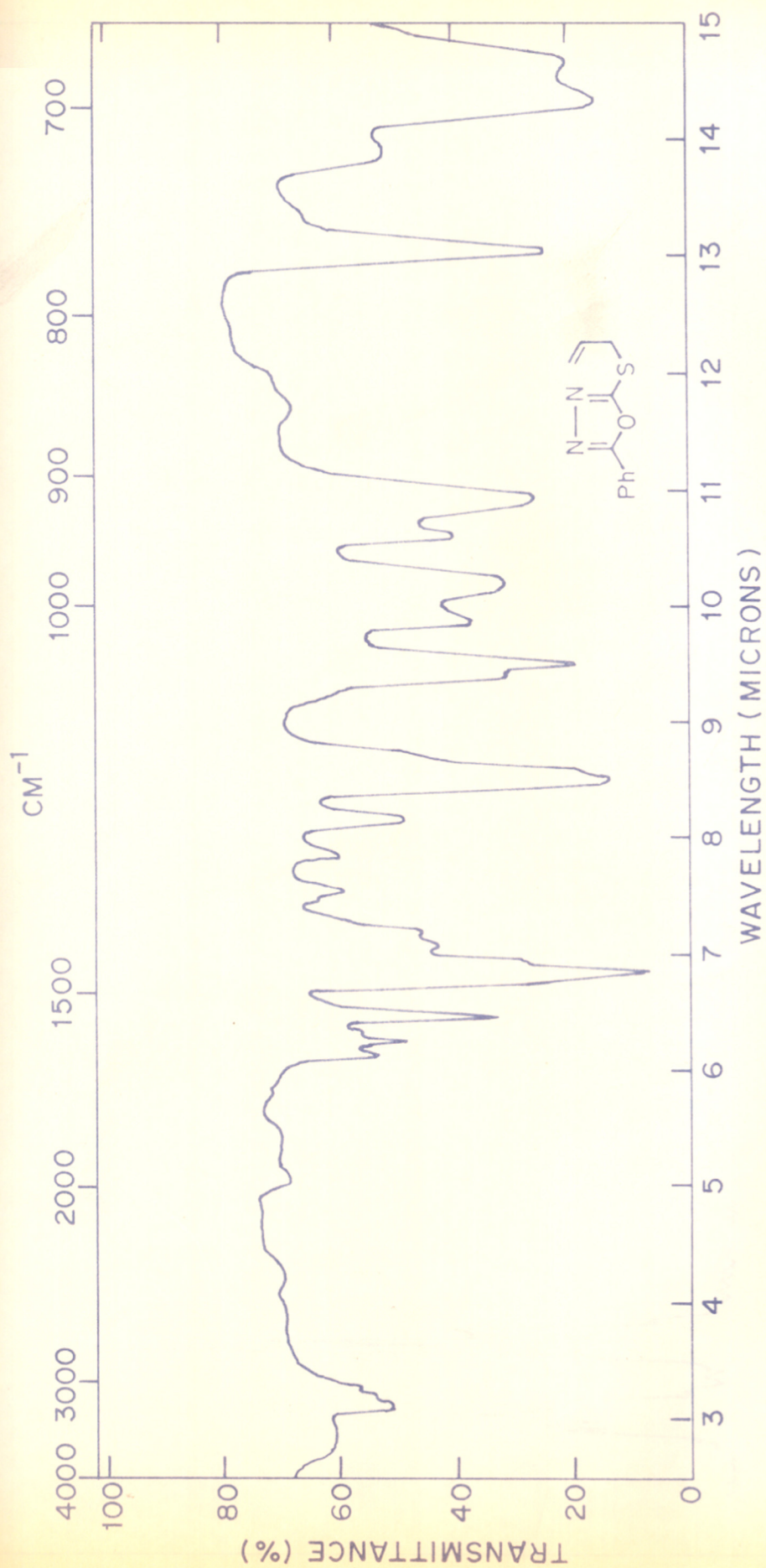


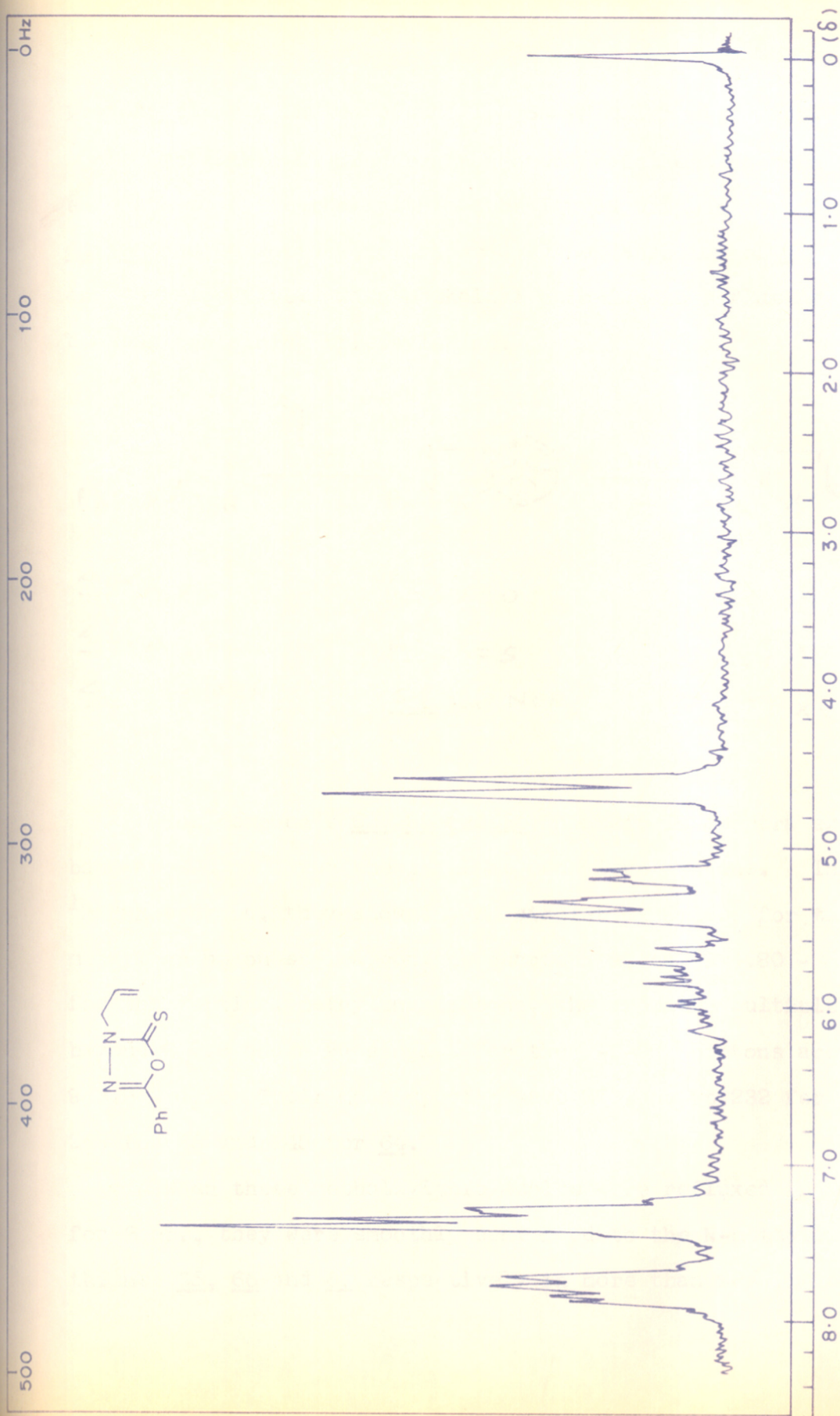
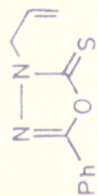
<u>41</u> : X = O	<u>56</u> : X = O	<u>59</u> : X = O
<u>42</u> : X = S	<u>57</u> : X = S	<u>60</u> : X = S
<u>43</u> : X = NCH ₃	<u>58</u> : X = NCH ₃	<u>61</u> : X = NCH ₃

Compounds 56, 57 and 58 gave IR bands at ca. 910-15 cm⁻¹ for the terminal methylene group. Their ¹H NMR spectra exhibited aromatic proton multiplets beyond δ 7.0, the 2-terminal methylene protons as ABX multiplet at ca. δ 5.0 - 5.5, a 1H multiplet for the olefinic proton at ca. δ 5.7 - 6.3, and a doublet for S-methylene protons at ca. δ 3.80 - 4.03. The mass spectra showed M⁺ ions at 218 for 56, 234 for 57 and 231 for 58.

When these thiazolyl azoles were thermolysed in refluxing DMF for 3 hr, the 1,3-S → N migration proceeded smoothly and 59, 60 and 61 were obtained in more than 85% yields.

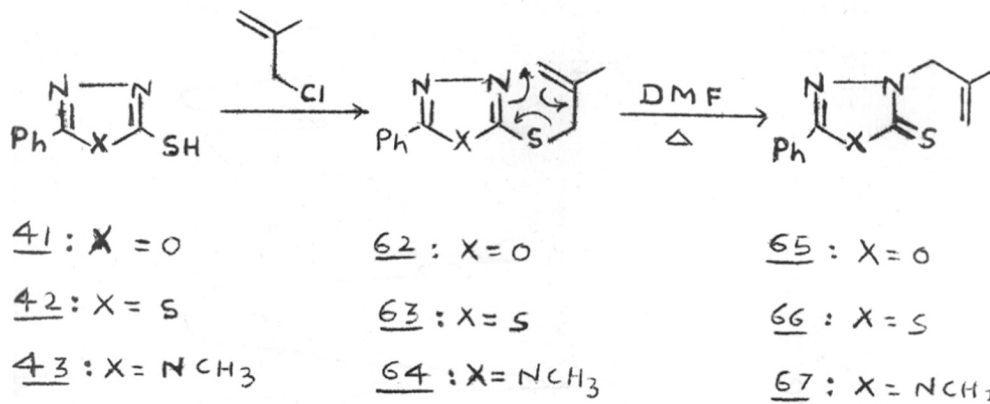
The compounds 59, 60 and 61 gave M⁺ ions at 218, 234 and 231 respectively in their mass spectra. Their IR showed bands at 1660 cm⁻¹ for C=C groupings and around 900-920 cm⁻¹ for the terminal methylene group. Their ¹H NMR spectra exhibited aromatic multiplets beyond δ 7.1, ABX multiplets for the terminal methylene protons at ca. δ 5.1 - 5.5, 1H multiplet for the olefinic proton at ca. δ 5.6 - 6.3 and most significantly a 2H doublet for the -N-CH₂-group at δ 4.63 for 59, δ 4.93 for 60 and δ 4.70 for 61. This deshielding of the methylene





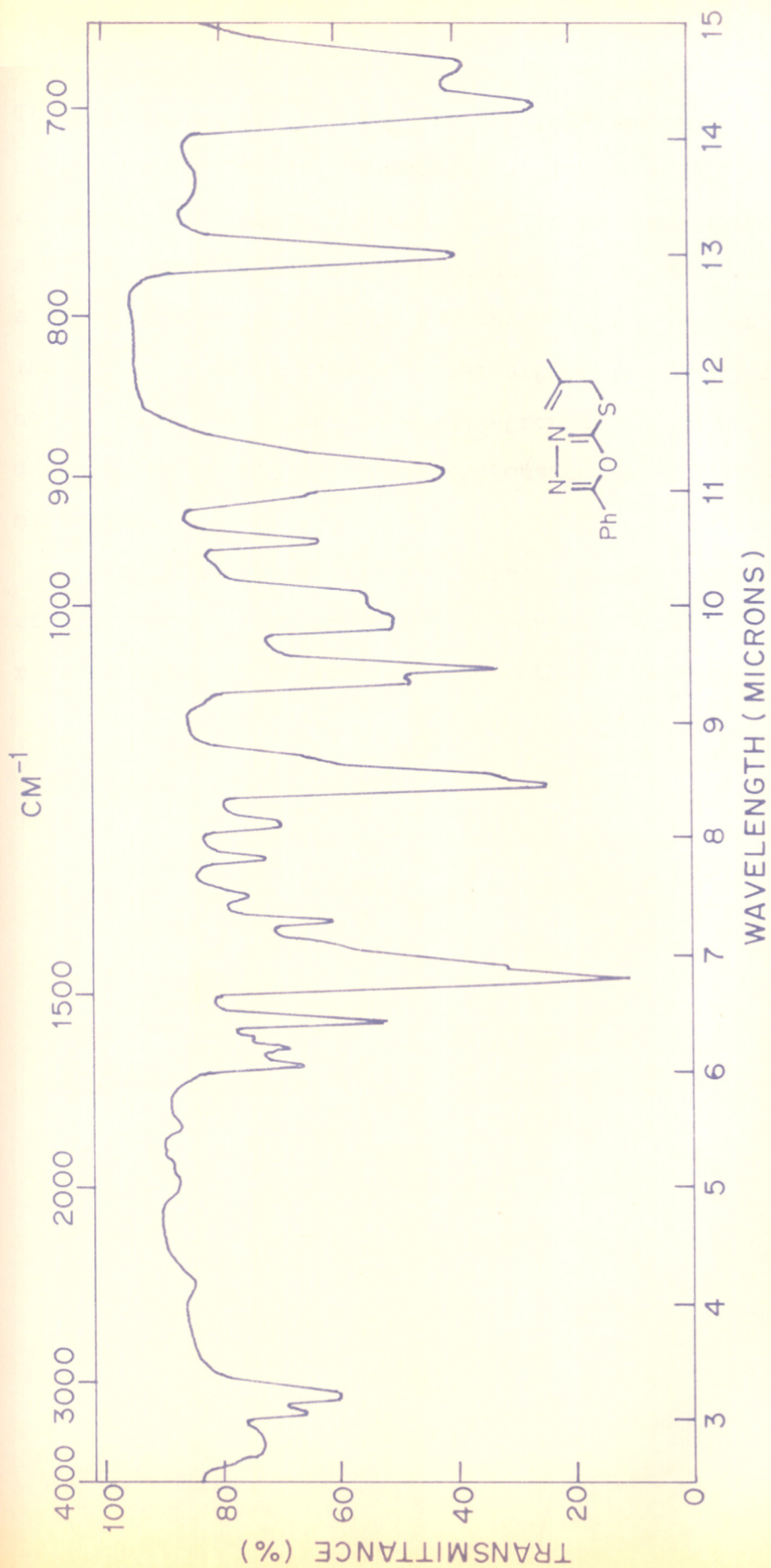
protons clearly indicated the 1,3 S $\rightarrow$ N allyl migration.

This thio-Claisen rearrangement reaction was then further extended to the methallylthio substituted triheteroatomic azoles 62, 63 and 64 which were prepared by condensation of 41, 42 and 43 respectively with methallyl chloride in refluxing benzene containing triethylamine.



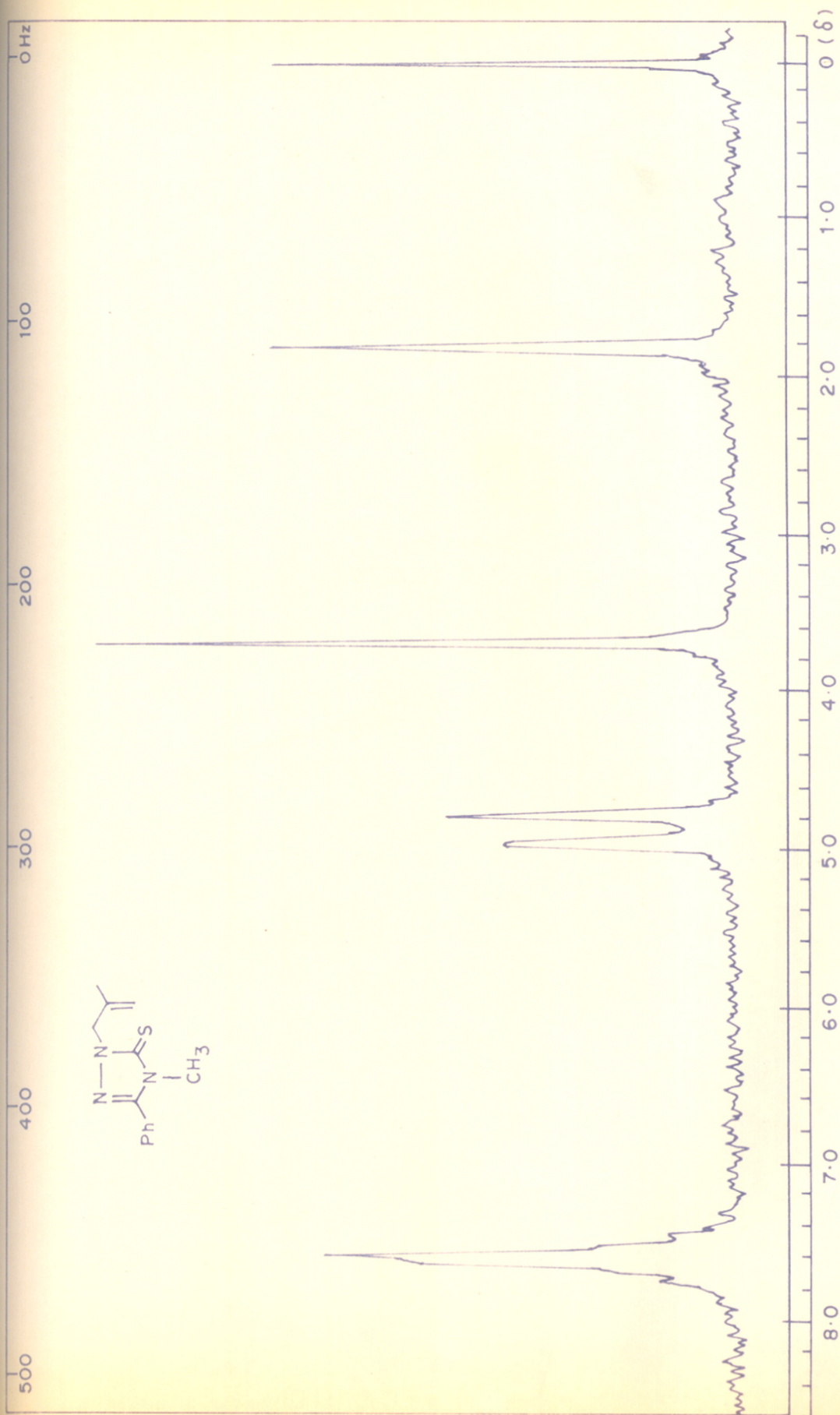
The compounds 62, 63 and 64 in their IR spectra exhibited a band at 890 cm⁻¹ for the terminal methylene protons. In their ¹H NMR spectra, they showed a 3H singlet at δ 1.96 for the methyl group on sp² carbon, AB quartets at ca. δ 4.80 - 5.20 for the terminal methylene protons, the aromatic multiplets beyond δ 7.2 and a 2H singlet for the -S-CH₂ protons around δ 3.9 - 4.1. Their mass spectra gave M⁺ ions at 232 for 62, 248 for 63 and 245 for 64.

When these methallylthio azoles were refluxed in DMF for 3 hr., they were smoothly converted to the N-methallyl thiones 65, 66 and 67 respectively in more than 90% yields.



The compounds 65, 66 and 67 in their IR spectra showed bands at ca. 1660 cm^{-1} and $890\text{-}900\text{ cm}^{-1}$. Their ^1H NMR spectra exhibited multiplets for the aromatic protons beyond $\delta\ 7.30$, a singlet for 2-terminal methylene protons at ca. $\delta\ 4.9 - 5.1$, a 3H singlet at ca. $\delta\ 1.80$ for the methyl group attached to the unsaturated carbon, and most significantly, a 2H singlet at ca. $\delta\ 4.7 - 4.8$ for the $-\text{N}-\text{CH}_2$ -grouping. Again, the deshielding of the methylene protons confirms the $\text{S} \rightarrow \text{N}$ migration.

As these thio-Claisen rearrangements of imino allylthio ethers proceed very smoothly, it may be speculated that these reactions can be extended to many other heterocyclic systems.

^1H NMR OF COMPOUND 67

EXPERIMENTAL

General method for the preparation of 2-alkylthio-5-phenyl-1,3,4-oxadiazoles, 2-alkylthio-5-phenyl-1,3,4-thiadiazoles and 5-alkylthio-4-methyl-3-phenyl-1,2,4-triazoles

A mixture of 2-mercapto-5-phenyl-1,3,4-oxadiazole 41 or 2-mercapto-5-phenyl-1,3,4-thiadiazole 42 or 5-mercapto-4-methyl-3-phenyl-1,2,4-triazole 43 (0.01 M), the relevant alkyl halide (chloride or bromide) (0.01 M) and triethylamine (0.01 M) was refluxed in benzene (50 ml) for 3 hr. The reaction mixture was then washed successively with water, 10% sodium hydroxide solution and again with water and finally dried (Na_2SO_4). The respective alkylthio substituted triheteroatomic azoles were obtained either by crystallization or by chromatography of the residue remaining after evaporation of benzene.

Compound 44: Crystallized from pet. ether.

Yield: 60%; m.p. 109° .

Elemental analyses: Found, C: 61.20%; H: 5.32%; N: 10.36%.

$\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$ requires, C: 61.31%; H: 5.11%; N: 10.22%.

IR ($\nu_{\text{max}}^{\text{nujol}}$): 1710 (C = O).

^1H NMR (CCl_4): 1.63 - 3.20 (m, 8H, methylene protons); 4.5 - 5.0 (ABX q, 1H, methine proton); 7.33 - 8.10 (m, 5H, aromatic).

Mass: 274 (M^+ ion).

Compound 45: Crystallized from pet. ether

Yield: 50%; m.p. 114° .

Elemental analyses: Found, C: 58.25%; H: 4.67%; N: 9.69%.

$C_{14}H_{14}N_2OS_2$ requires, C: 57.93%; H: 4.83%;
N: 9.65%.

IR ($\nu_{\max}^{\text{nujol}}$): 1705 (C = O).

1H NMR (CCl_4): 1.60 - 3.06 (m, 8H, methylene protons); 4.60-5.06
(ABX q, 1H, methine proton); 7.23 - 8.0
(m, 5H, aromatic).

Mass: 290 (M^+ ion).

Compound 46: Obtained by chromatography (silica gel, 1:20;
benzene + ethyl acetate 9:1)
Yield: 65% as an oil.

Elemental analyses: Found, C: 62.44%; H: 5.78%; N: 14.80%.

$C_{15}H_{17}N_3OS$ requires, C: 62.72%; H: 5.92%;
N: 14.63%.

IR ($\nu_{\max}^{\text{liq.film}}$): 1715 (C = O).

1H NMR (CCl_4): 1.60 - 2.83 (m, 8H, methylene protons); 3.56
(s, 3H, methyl); 4.26 - 4.76 (ABX q, 1H, methine
proton); 7.10 - 7.70 (m, 5H, aromatic).

Mass: 287 (M^+ ion).

Compound 48: Crystallized from chloroform + benzene mixture.
Yield: 85%; m.p. 168°.

Elemental analyses: Found, C: 64.81%; H: 4.29%; N: 9.32%

Elemental analyses: $C_{16}H_{12}N_2O_2S$ requires, C: 64.86%; H: 4.05%;
N: 9.46%.

IR ($\nu_{\max}^{\text{nujol}}$): 1670 (C = O).

$^1\text{H NMR}$ (CDCl_3) : 4.96 (s, 2H, methylene); 7.36 - 8.20
(m, 10H, aromatic).

Mass: 296 (M^+ ion).

Compound 49: Crystallized from chloroform + benzene mixture.

Yield: 70%; m.p. 152° .

Elemental analyses: Found, C: 61.84%; H: 3.97%; N: 8.73%.

$\text{C}_{16}\text{H}_{12}\text{N}_2\text{OS}_2$ requires, C: 61.54%; H: 3.85%;
N: 8.97%.

$\text{IR}(\nu_{\text{max}}^{\text{nujol}})$: 1670 (C = O).

$^1\text{H NMR}$ (CDCl_3): 4.86 (s, 2H, methylene protons); 7.16 - 7.90
(m, 10H, aromatic).

Mass: 312 (M^+ ion).

Compound 50 : Crystallized from pyridine + benzene mixture.

Yield: 90%; m.p. 216° .

Elemental analyses: Found, C: 65.78%; H: 4.77%; N: 13.64%.

$\text{C}_{17}\text{H}_{15}\text{N}_3\text{OS}$ requires, C: 66.02%; H: 4.85%;
N: 13.59%.

$\text{IR}(\nu_{\text{max}}^{\text{nujol}})$: 1670 (C = O).

$^1\text{H NMR}$ (pyridine): 3.53 (s, 3H, methyl); 5.16 (s, 2H, methylene).

Mass: 309 (M^+ ion).

Compound 56: Obtained by chromatography (silica gel, 1:20;
benzene + ethylacetate 19:1).

Yield: 80% as an oil.

Elemental analyses: Found, C: 60.71%; H: 4.39%; N: 12.99%.

$\text{C}_{11}\text{H}_{10}\text{N}_2\text{OS}$ requires, C: 60.55%; H: 4.59%;
N: 12.84%.

$\text{IR}(\nu_{\text{max}}^{\text{liq film}})$: 910 (C = CH_2); 1645 (C = C).

^1H NMR (CCl_4): 3.93 (d, $J = 7$ Hz; 2H, S- CH_2 protons); 5.06 - 5.66 (ABX m, 2H, C = CH_2 protons); 5.73 - 6.30 (m, 1H, -CH = proton); 7.26 - 8.13 (m, 5H, aromatic).

Mass: 218 (M^+ ion).

Compound 57 : Obtained by chromatography (silica gel, 1:20; benzene + ethyl acetate, 5:1).

Needles from pet. ether.

Yield: 75%; m.p. 44° .

Elemental analyses: Found, C: 56.30%; H: 4.16%; N: 12.08%.

$\text{C}_{11}\text{H}_{10}\text{N}_2\text{S}_2$ requires, C: 56.41%; H: 4.27%;
N: 11.96%.

IR ($\nu_{\text{max}}^{\text{nujol}}$): 915 (C = CH_2); 1650 (C = C).

^1H NMR (CCl_4): 4.0 (d, $J = 7$ Hz; 2H, S- CH_2 protons); 5.03 - 5.60 (ABX m, 2H, C = CH_2 protons); 5.70 - 6.33 (m, 1H, -CH = proton); 7.23 - 8.13 (m, 5H, aromatic).

Mass: 234 (M^+ ion).

Compound 58 : Obtained by chromatography (silica gel, 1:20; benzene + ethyl acetate, 5:3). Crystallized from pet. ether into needles.

Yield: 55%; m.p. 78° .

Elemental analyses: Found, C: 62.07%; H: 5.55%; N: 18.41%.

$\text{C}_{12}\text{H}_{13}\text{N}_3\text{S}$ requires, C: 62.34%; H: 5.63%;
N: 18.18%.

IR ($\nu_{\text{max}}^{\text{nujol}}$): 910 (C = CH_2).

^1H NMR (CCl_4): 3.60 (s, 3H, N- CH_3 protons); 3.86 (d, $J = 7$ Hz; 2H, S- CH_2 protons); 4.96 - 5.46 (ABX m, 2H, C= CH_2 protons); 5.63 - 6.26 (m, 1H, -CH = proton); 7.33 - 7.80 (m, 5H, aromatic).

Mass: 231 (M^+ ion).

Compound 62 : Obtained by chromatography (silica gel, 1:20; benzene)

Yield: 90% as an oil.

Elemental analyses: Found, C: 62.11%; H: 5.31%; N: 11.84%.

$C_{12}H_{12}N_2OS$ requires, C: 62.07%; H: 5.17%;
N: 12.07%.

$IR(\nu_{\max}^{\text{liq.film}})$: 890 (C = CH₂)

1H NMR(CCl₄): 1.96 (s, 3H, methyl); 3.93 (s, 2H, methylene protons)
4.86 - 5.23 (AB q, 2H, C = CH₂ protons);
7.3 - 8.13 (m, 5H, aromatic).

Mass: 232 (M⁺ ion).

Compound 63 : Obtained by chromatography (silica gel, 1:20; benzene + ethyl acetate, 19:1). Crystallized from pet.ether.

Yield: 80%; m.p. 56°.

Elemental analyses: Found, C: 58.01%; H: 4.76%; N: 11.34%.

$C_{12}H_{12}N_2S_2$ requires, C: 58.06%; H: 4.84%;
N: 11.29%.

$IR(\nu_{\max}^{\text{nujol}})$: 890 (C = CH₂).

1H NMR(CCl₄): 1.96 (s, 3H, methyl); 4.1 (s, 2H, methylene protons); 4.86 - 5.23 (AB q, 2H, C = CH₂ protons),
7.33 - 8.10 (m, 5H, aromatic).

Mass: 248 (M⁺ ion)

Compound 64 : Crystallized from pet.ether .

Yield: 70%; m.p. 81°.

Elemental analyses: Found, C: 63.55%; H: 6.06%; N: 17.32%

$C_{13}H_{15}N_3S$ requires, C: 63.67%; H: 6.12%;
N: 17.14%.

$IR(\nu_{\max}^{\text{nujol}})$: 890 (C = CH₂).

1H NMR(CCl₄) : 1.96 (s, 3H, C = C-CH₃); 3.63 (s, 3H, N-CH₃ protons); 4.80 - 5.10 (ABq, 2H, C = CH₂ protons);
7.33 - 7.90 (m, 5H, aromatic).

General method of thermolysis of the alkylthio substituted triheteroatomic azoles

An alkylthio substituted triheteroatomic azole (0.005M) was refluxed in 10 ml dry DMF for 5 hr. The solvent was then removed under high vacuum. The tarry residue remaining in the flask was then chromatographed over silica gel column (1:20).

Thermolysis of 44

Elusion with pet. ether + benzene (1:1) gave the compound 47 (30%) while the compound 41 came in benzene + ethylacetate (3:1) (15%).

Compound 47 : m.p. 148° (pet. ether).

Elemental analysis: Found, C: 61.43%; H: 5.29%; N: 10.24%.

$C_{14}H_{14}N_2O_2S$ requires, C: 61.31%; H: 5.11%;
N: 10.22%.

IR($\nu_{\text{max}}^{\text{nujol}}$) : 1735 (C = O).

1H NMR (CCl_4): 1.90 - 2.80 (m, 8H, methylene protons); 5.10 - 5.55 (ABX q, 1H, methine proton); 7.33 - 8.0 (m, 5H, aromatic).

Mass: 274 (M^+ ion).

Thermolysis of 45

Elusion with benzene + ethyl acetate (2:1) gave the compound 42 (10%).

Thermolysis of 46

Elusion with benzene + ethyl acetate (1:1) gave the compound 43 (20%).

Thermolysis of 48

Elution with pet.ether gave the compound 51 (5%) while the benzene + ethyl acetate (3:1) fractions gave the compound 41 (20%).

Compound 51 : n.p. 132° (pet.ether).

Elemental analyses: Found, C: 65.10%; H: 4.17%; N: 9.58%.

$C_{16}H_{12}N_2O_2S$ requires, C: 64.86%; H: 4.05%;
N: 9.46%.

IR ($\nu_{\max}^{\text{nujol}}$): 1700 (C = O).

1H NMR (CCl_4): 5.40 (s, 2H, methylene protons); 7.16 - 8.00
(m, 10H, aromatic).

Mass: 296 (M^+ ion).

Thermolysis of 49

Elution with pet.ether gave the compound 52 (3%) while 42 (30%) was obtained by the evaporation of benzene + ethyl acetate (2:1) fraction.

Compound 52 : n.p. 196° (pet.ether).

Elemental analyses: Found, C: 61.33%; H: 3.91%; N: 9.14%.

$C_{16}H_{12}N_2OS_2$ requires, C: 61.54%; H: 3.85%;
N: 8.97%.

IR ($\nu_{\max}^{\text{nujol}}$) : 1700 (C = O).

1H NMR ($CDCl_3$): 5.60 (s, 2H, methylene protons); 7.23 - 8.06
(m, 10H, aromatic).

Mass: 312 (M^+ ion).

Thermolysis of 50

Elusion with pet. ether + benzene (19:1) gave the compound 53 (7%) while the compound 13 (25%) was obtained from benzene + ethyl acetate (1:1) fraction.

Compound 53 : m.p. 146° (pet.ether).

Elemental analyses: Found, C: 66.11%; H: 4.63%; N: 13.44%.

$C_{17}H_{15}N_3OS$ requires, C: 66.02%; H: 4.85%;
N: 13.59%.

IR($\nu_{\max}^{\text{nujol}}$) : 1700 (C = O).

1H NMR (CCl_4): 3.60 (s, 3H, methyl); 5.46 (s, 2H, methylene protons); 7.13 - 8.0 (m, 10H, aromatic).

Mass: 309 (M^+ ion).

Thermolysis of 56

The compound 59 (90%) was obtained from pet.ether + benzene (1:1) fraction.

Compound 59: m.p. 95° (pet.ether).

Elemental analysis: Found, C: 60.64%; H: 4.49%; N: 12.96%.

$C_{11}H_{10}N_2OS$ requires, C: 60.55%; H: 4.59%;
N: 12.84%.

IR($\nu_{\max}^{\text{nujol}}$) : 910 (C = CH_2); 1660 (C = C).

1H NMR (CCl_4): 4.63 (d, J = 6 Hz; 2H, N - CH_2 protons); 5.1 - 6.2 (ABX m, 3H, CH = CH_2); 7.13 - 8.0 (m, 5H, aromatic).

Mass: 218 (M^+ ion)

Thermolysis of 57

Elusion with pet.ether gave the compound 60 (85%).

Compound 60 : m.p. 69° (pet.ether).

Elemental analyses: Found, C: 56.20%; H: 4.33%; N: 12.16%.

$C_{11}H_{10}N_2S_2$ requires, C: 56.41%; H: 4.27%;
N: 11.96%.

IR ($\nu_{\max}^{\text{nujol}}$) : 910 (C = CH₂); 1660 (C = C).

¹H NMR (CCl₄): 4.93 (d, J = 6 Hz; 2H, N-CH₂ protons);
5.13 - 6.36 (ABX m, 3H, CH = CH₂); 7.2 - 7.76
(m, 5H, aromatic).

Mass: 234 (M⁺ ion).

Thermolysis of 58

The compound 61 (95%) was obtained by the evaporation of benzene fraction as an oil.

Compound 61

Elemental analyses: Found, C: 62.38%; H: 5.78%; N: 18.28%.

$C_{12}H_{13}N_3S$ requires, C: 62.34%; H: 5.63%;
N: 18.13%.

IR ($\nu_{\max}^{\text{liq.film}}$) : 915 (C = CH₂); 1660 (C = C).

¹H NMR (CCl₄): 3.50 (s, 3H, methyl); 4.70 (d, J = 6 Hz; 2H;
N - CH₂ protons); 4.96 - 6.23 (ABX m, 3H,
CH = CH₂); 7.16 - 7.56 (m, 5H, aromatic).

Mass: 231 (M⁺ ion).

Thermolysis of 62

The compound 65 (96%) was obtained from pet.ether + benzene (1:1) fraction.

Compound 65 : m.p. 102° (pet.ether).

Elemental analyses: Found, C: 62.00%; H: 5.34%; N: 12.14%.

$C_{12}H_{12}N_2OS$ requires, C: 62.07%; H: 5.17%;

N: 12.07%.

IR ($\nu_{\max}^{\text{nujol}}$): 895 (C = CH₂); 1660 (C = C).

¹H NMR (CCl₄): 1.83 (s, 3H, methyl); 4.63 (s, 2H, C = CH₂);

5.0 (s, 2H, N-CH₂), 7.23 - 8.16 (m, 5H, aromatic).

Mass: 232 (M⁺ ion).

Thermolysis of 63

Elution with pet.ether gave the compound 66 (90%).

Compound 66 : m.p. 98° (pet. ether).

Elemental analyses: Found, C: 58.36%; H: 4.92%; N: 11.03%.

$C_{12}H_{12}N_2S_2$ requires, C: 58.06%; H: 4.84%;

N: 11.29%.

IR ($\nu_{\max}^{\text{nujol}}$): 900 (C = CH₂); 1660 (C = C).

¹H NMR (CCl₄): 1.83 (s, 3H, methyl); 4.93 (broad s, 4H, N-CH₂ and C = CH₂ protons); 7.30 - 7.80 (m, 5H, aromatic).

Mass: 248 (M⁺ ion).

Thermolyses of 64

Compound 67 (95%) was obtained from benzene fraction.

Compound 67 : m.p. 86° (pet. ether).

Elemental analyses: Found, C: 63.79%; H: 6.26%; N: 17.31%.

$C_{13}H_{15}N_3S$ requires, C: 63.67%; H: 6.12%;
N: 17.14%.

IR($\nu_{\max}^{\text{nujol}}$): 900 (C = CH₂); 1660 (C = C).

1H NMR (CCl₄): 1.80 (s, 3H, C = C - CH₃); 3.66 (s, 3H, N-CH₃ protons); 4.80 (s, 2H, C = CH₂); 4.93 (s, 2H, N - CH₂ protons); 7.33 - 7.86 (m, 5H, aromatic).

Mass: 245 (M⁺ ion).

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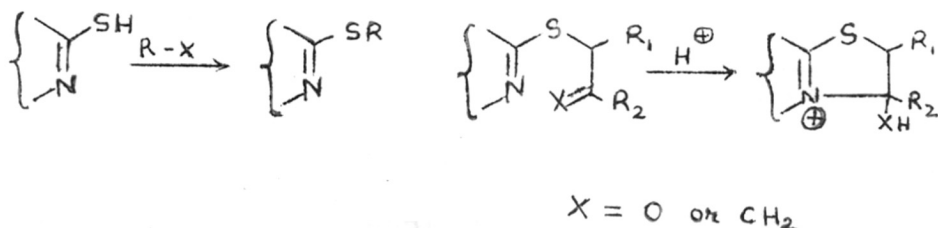
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CHAPTER III

SYNTHESIS OF FUSED TRIHETEROATOMIC AZOLE RING SYSTEMS

INTRODUCTION

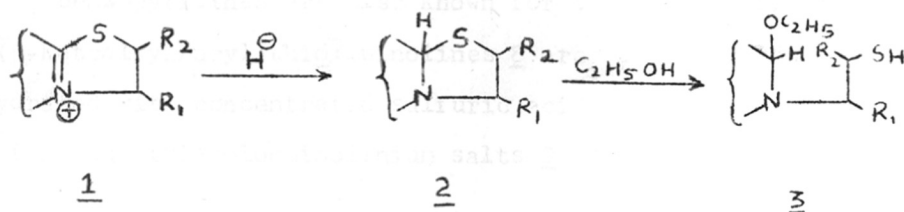
Many heterocyclic iminothiols, in which the imino group is a part of the ring system, are reported to react easily with alkyl halides, under basic conditions and from the imino thioethers in which the substitution takes place on S in preference to N.



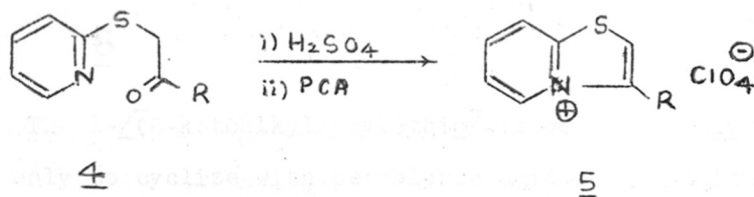
When the alkyl group in such imino alkylthioethers contains a β -keto group or a β - γ -unsaturation, they are known to cyclize in acidic medium and form the fused thiazolium ring system. The cyclization is generally achieved with sulfuric acid, hydrobromic acid, polyphosphoric acid or perchloric acid (PCA). The ease of cyclization depends on the nucleophilicity of imino nitrogen.

Depending on the acid employed in the reaction, a cyclized or a cyclodehydrated product is obtained. Generally, perchloric acid in methanol brings about only cyclization while the other acids mentioned above complete even the cyclodehydration. The cyclized as well as cyclodehydrated products are usually isolated as their perchlorate salts.

These fused thiazolium salts 1 when reacted with sodium borohydride or lithium aluminium hydride are reduced at the imonium $-C = \overset{+}{N}-$, the electrophilic bridgehead carbon being attacked by the hydride ion; however, this product 2 is usually unstable and ring opening takes place to form N-substituted saturated heterocycles 3 (1).

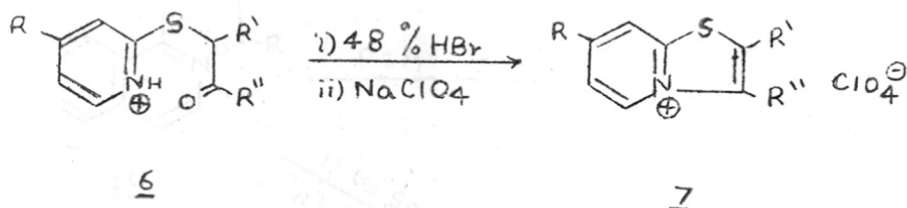


Bradsher et al.(2) in 1964 reported the cyclodehydration of α -[β -ketoalkyl]thio γ -pyridines 4 with sulfuric acid followed by their isolation as thiazolopyridinium perchlorates 5.

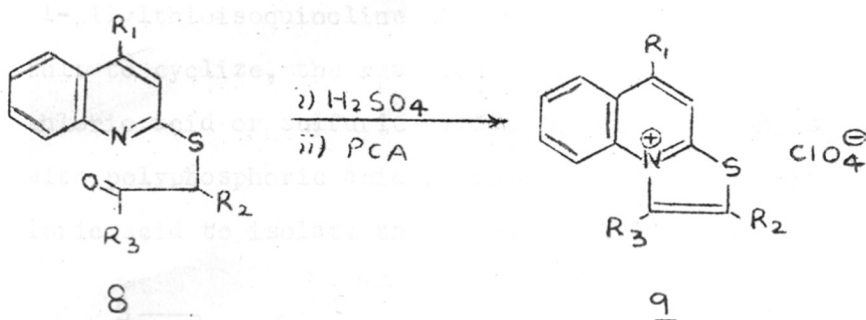


α -(β -ketoalkyl)thio pyridinium salts 6 can also be cyclodehydrated to thiazolopyridinium perchlorates 7 using 48% hydrobromic acid for 29-50 hr. followed by treatment with

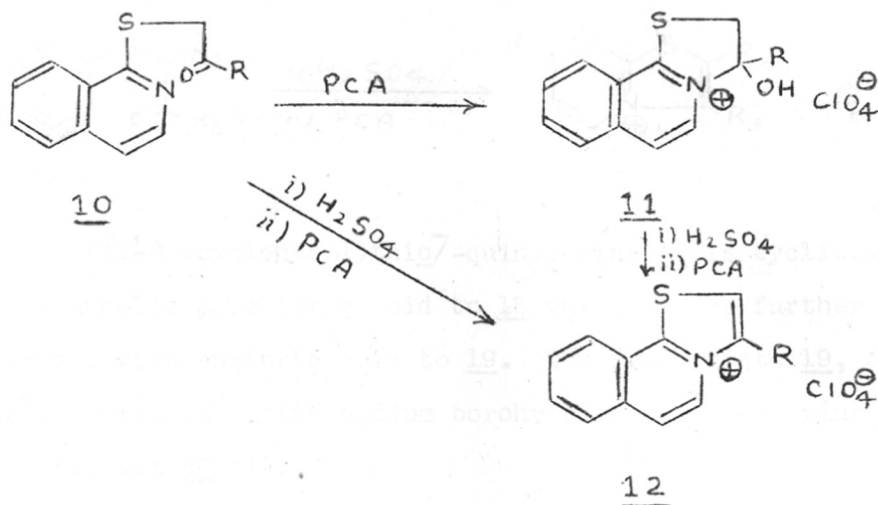
sodium perchlorate (3).



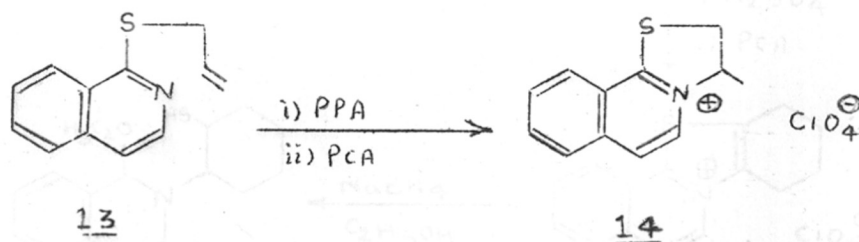
Benzopyridines are also known for such cyclizations. 2-[(β-Ketoalkyl/aryl)thio]quinolines 8 are easily cyclodehydrated with concentrated sulfuric acid at room temperature and form the thiazoloquinolinium salts 9 (4).



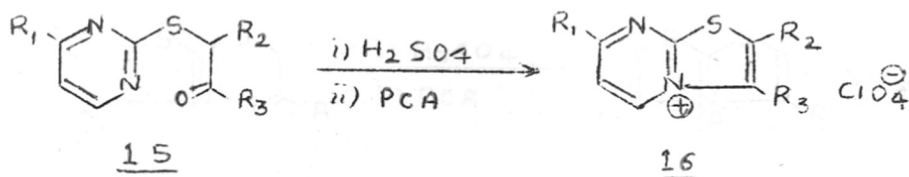
The 1-[(β-ketoalkyl/aryl)thio]-isoquinolines 10 are known only to cyclize with perchloric acid to 11 while cyclodehydrated thiazoloisoquinolinium perchlorates 12 are obtained by the action of sulfuric acid on 11 or directly on 10 (5).



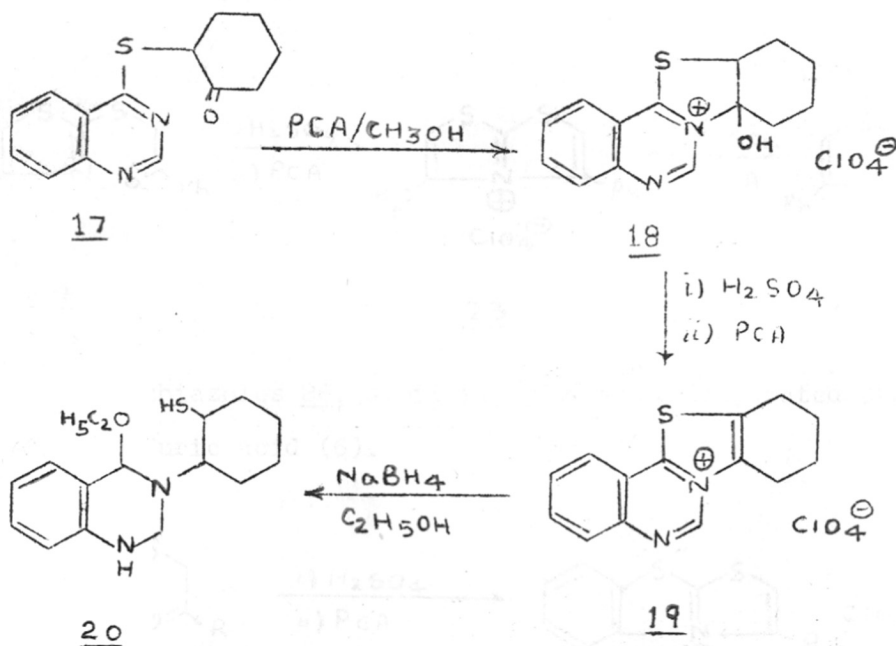
1-Allylthioisoquinoline **13**, on the other hand, is difficult to cyclize, the reaction failing with ethanolic hydrochloric acid or sulfuric acid. The cyclization is achieved only with polyphosphoric acid followed by treatment with perchloric acid to isolate the perchlorate **14** (5).



2-[β -Ketoalkyl/aryl]thio-7-pyrimidines and their 4-substituted derivatives **15** are readily cyclodehydrated with sulfuric acid to **16** (6).

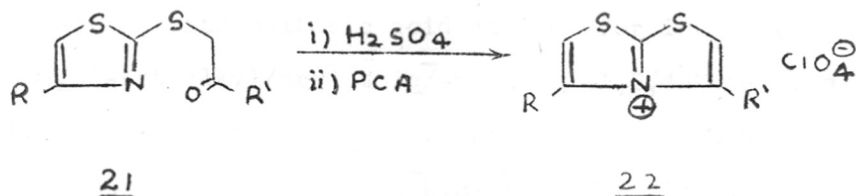


4-[(2-Oxocyclohexyl)thio]-quinazoline 17 is cyclized with methanolic perchloric acid to 18 which can be further dehydrated with sulfuric acid to 19. The perchlorate 19, on reduction with ethanolic sodium borohydride gives the ring opened product 20 (1).

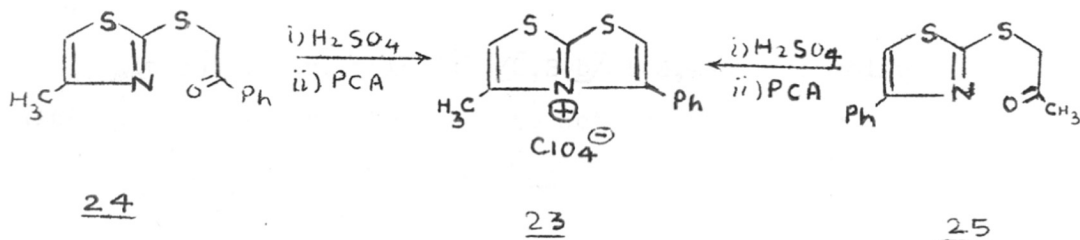


The 2-[(β -keto alkyl/aryl) thio]-thiazoles 21 are cyclodehydrated with concentrated sulfuric acid at 100° to

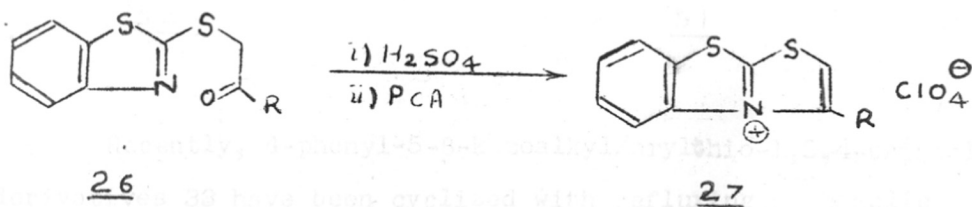
thiazolothiazolium perchlorates 22 (7).



The possibility that the cyclization was preceded by rearrangement was eliminated by preparation of 3-methyl-5-phenyl-thiazolo[2,3-b]thiazolium perchlorate 23 by cyclization of 2-phenacylthio-4-methyl-thiazole 24 as well as by cyclization of 2-acetylthio-4-phenyl-thiazole 25 (7).

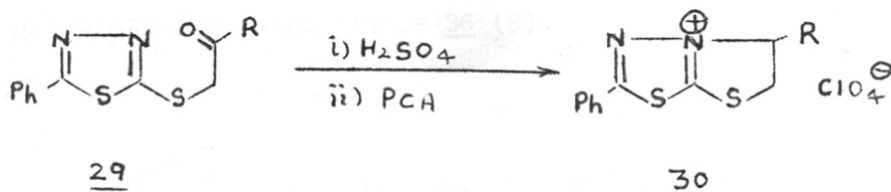


Benzothiazoles 26, similarly give cyclodehydrated products 27, with sulfuric acid (6).

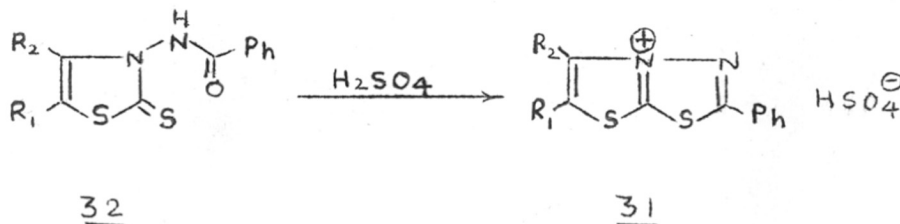


However, all attempts to cyclize 2-(β -ketoaryl)-thio-benzoxazole 28 failed, the starting material being recovered after treatment with sulfuric acid at 100° for 1 week (6).

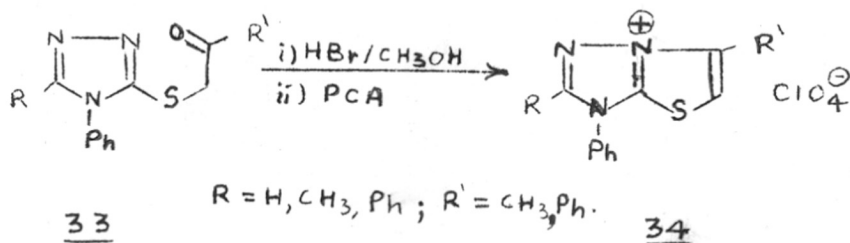
2-[β -ketoalkyl/aryl]thio-5-phenyl-1,3,4-thiadiazoles 29 with sulfuric acid are reported to give the unusual 5-alkyl/aryl-2-phenyl-5,6-dihydro-thiazolo [2,3-b] 1,3,4-thiadiazolium salts 30 (8).



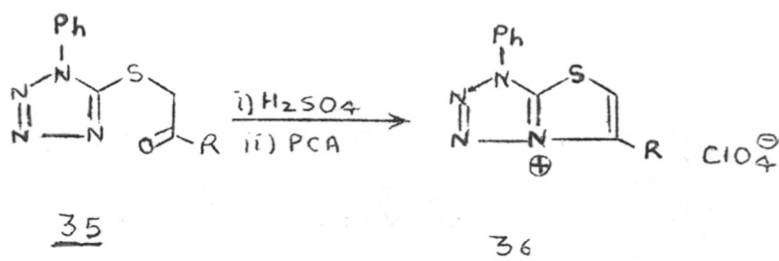
Alternatively, thiazolo [2,3-b] 1,3,4-thiadiazolium salts 31 are also prepared by the action of sulfuric acid on 3-benzoylamino-thiazol-2-thiones 32 (9).



Recently, 4-phenyl-5- β -ketoalkyl/arylthio-1,2,4-triazole derivatives 33 have been cyclized with refluxing methanolic hydrobromic acid to thiazolo [3,2-b] -1,2,4-triazolium salts 34 (10).



The 5-[(β -ketoalkyl/aryl)thio]-tetrazoles 35 similarly cyclize with concentrated sulfuric acid and form thiazolo [3,2-d]tetrazolium perchlorates 36 (8).

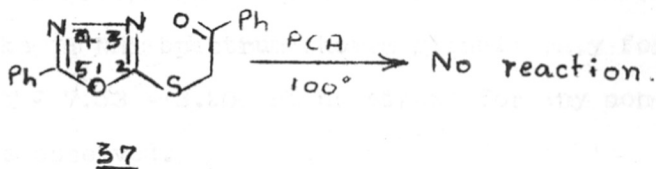


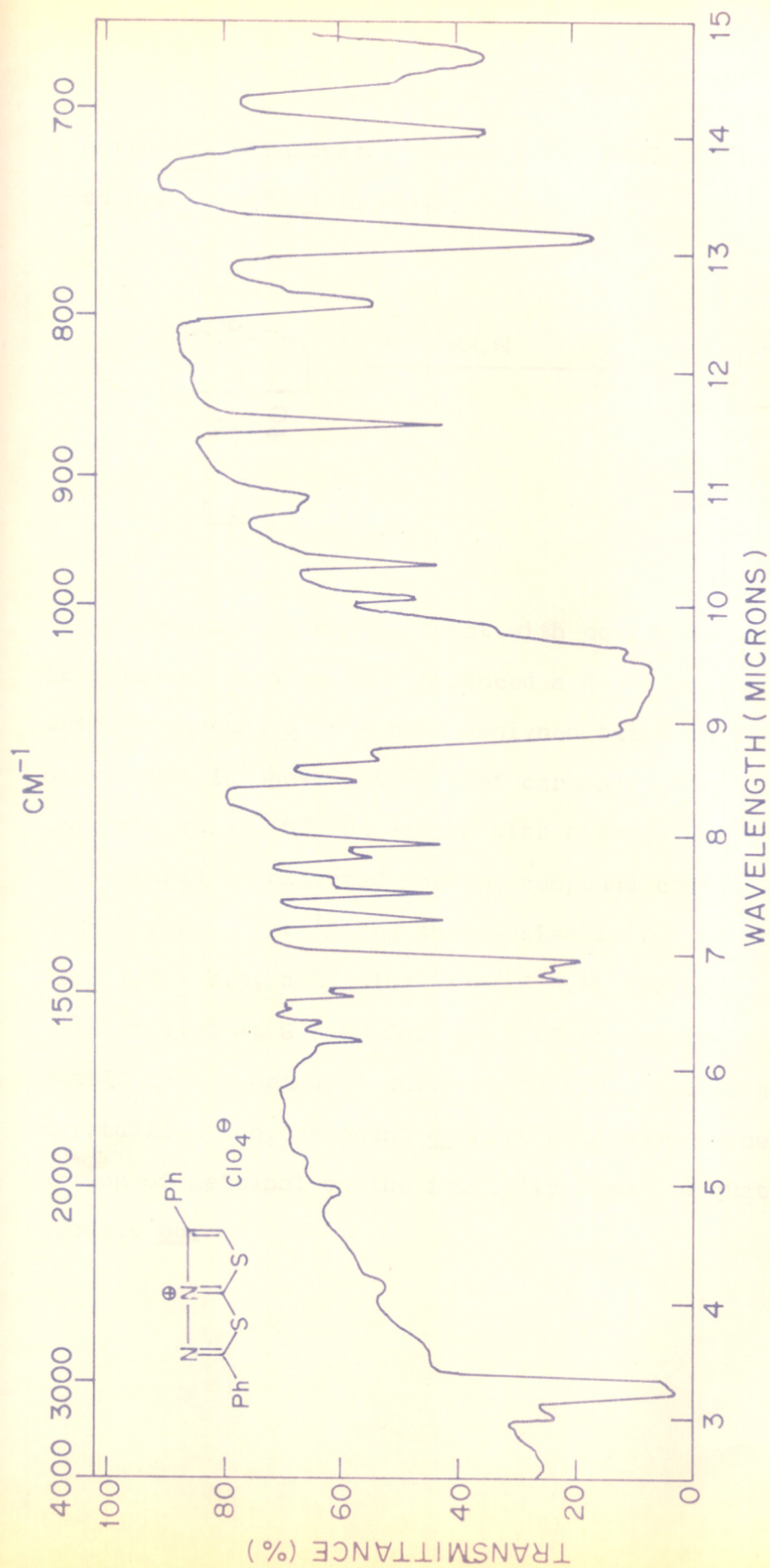
PRESENT WORK

From the foregoing discussion it is evident that the ease of cyclisation of various heterocyclic imino alkylthio ethers in which the alkyl group contains a β -keto grouping or a β -Y double bond depends on stereoelectronic factors affecting the ring N-atom at which cyclization occurs. As a part of our general study of the chemistry of triheteroatomic azoles, it was planned to study similar cyclisation on these ring systems and gain further insight into the reactivity, nucleophilicity of the ring N-atoms and the stability of the rings in such systems.

Attempted cyclization of 2-phenacylthio-5-phenyl-1,3,4-oxadiazole

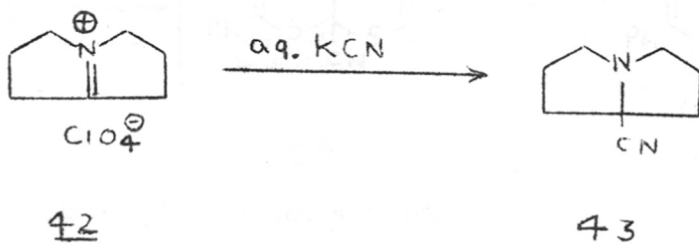
2-Phenacylthio-5-phenyl-1,3,4-oxadiazole 37 was observed to be very resistant to cyclization. Attempted cyclization of 37 with PCA for 15 hr. failed, the starting material being recovered after the reaction. This could be expected on account of the weak nucleophilicity of nitrogen at position 3 in 37. It, however, reacted with PCA at temperatures above 140° , but only to produce intractable tars.



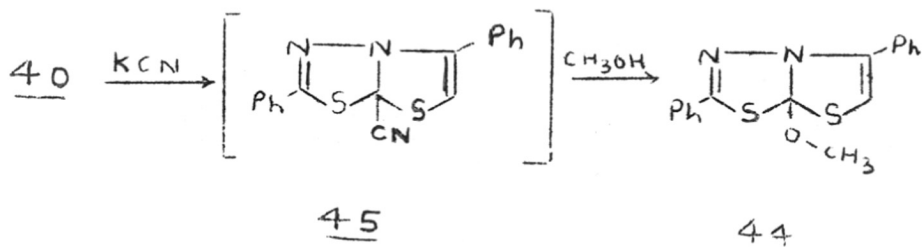


IR OF COMPOUND 40

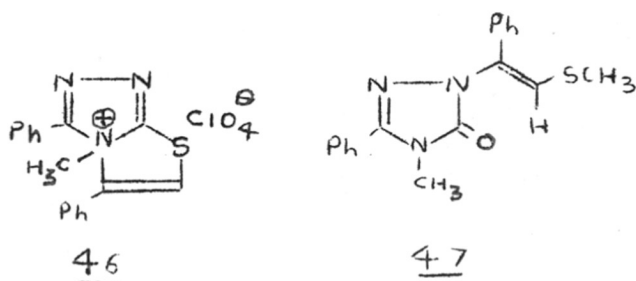
confirm its structure. Methanol was used due to the insolubility of 40 in water.



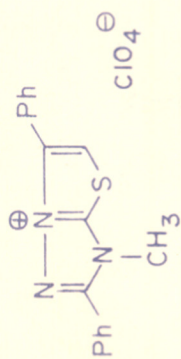
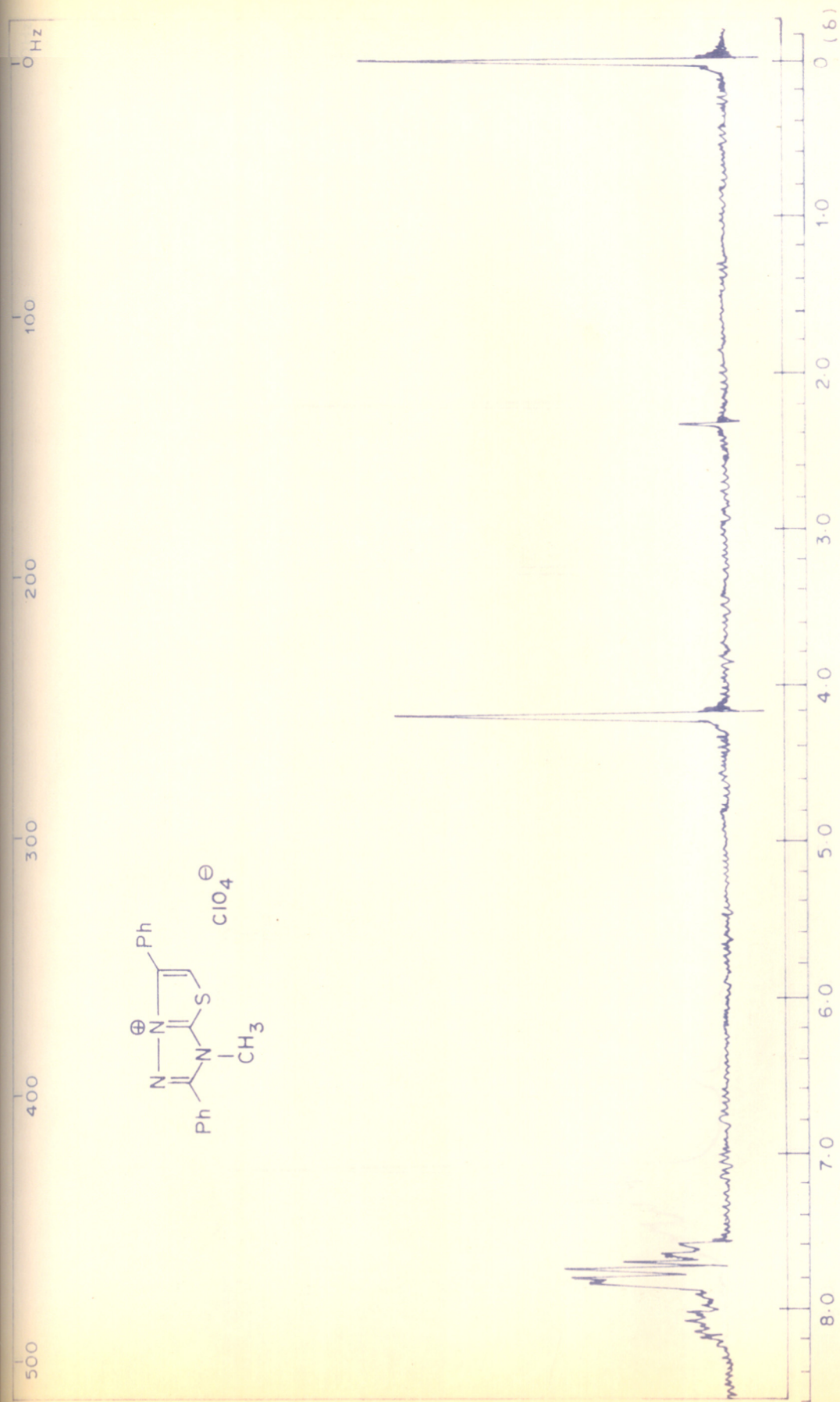
Compound 40 on treatment with equimolar amount of KCN in methanol as a solvent produced a dequaternized product, to which structure 44 has been assigned based on its spectral data. The IR showed absence of carbonyl group. The mass spectrum showed M^+ ion at 326 with a fragment ion at 295 ($M^+ - OCH_3$) as expected for the compound containing an $O-CH_3$ group. The 1H NMR showed signals for 10 aromatic protons at δ 7.0 - 7.6, a 3H singlet at δ 4.15 for the methyl group and a 1H singlet at δ 6.30 for the olefinic proton. Since 40 is stable to hot methanol which in fact is used as a solvent for crystallization, compound 44 must have been formed by the action of methanol on the initially formed dequaternized product 45.



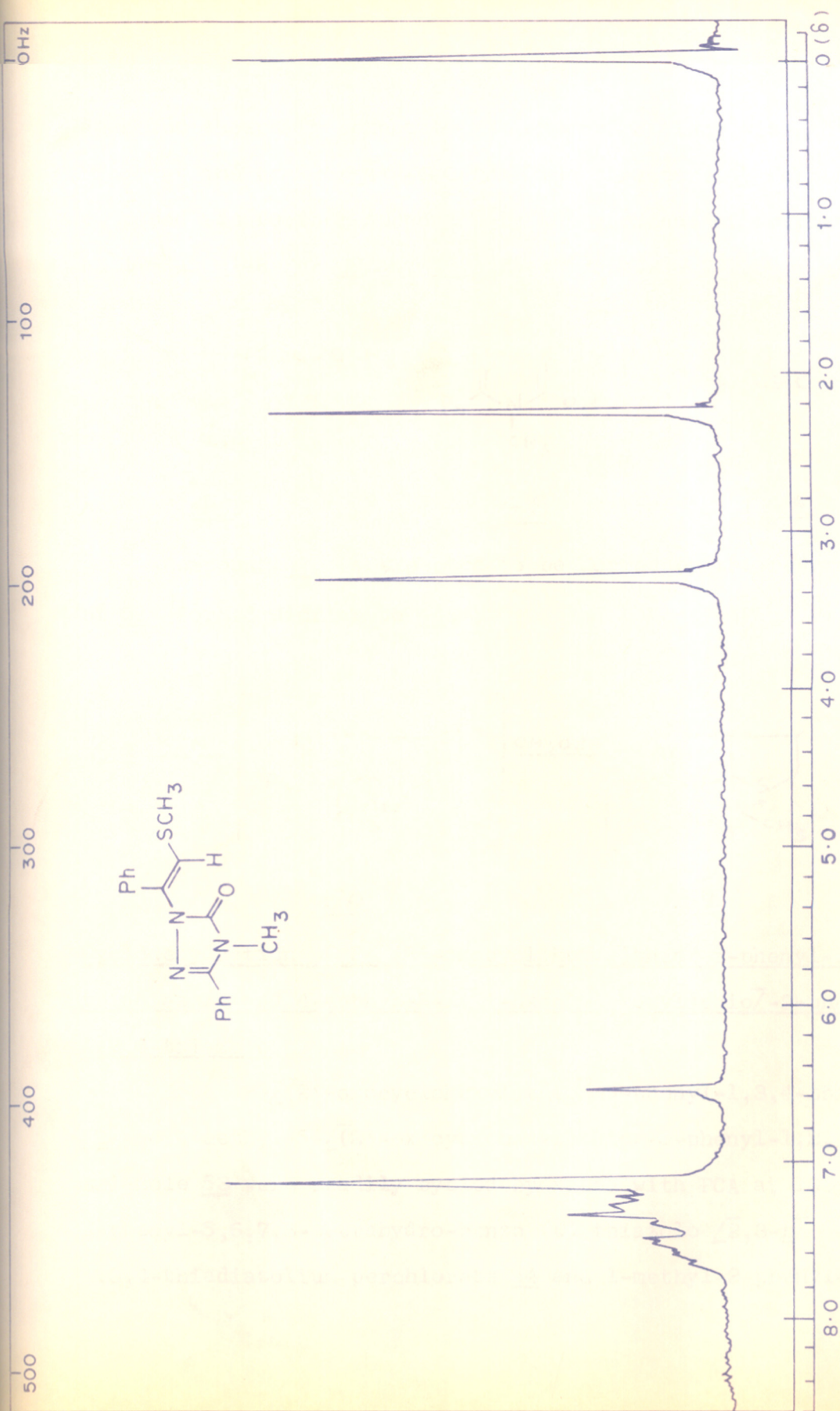
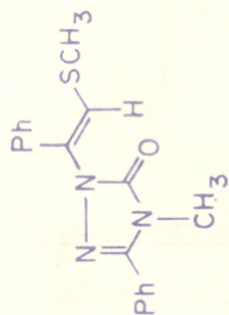
Compound 41 analysed satisfactorily for its elements. Its IR exhibited a broad band at $1060-1110 \text{ cm}^{-1}$ for ClO_4^- . Its ^1H NMR spectrum showed a 3H singlet at δ 4.23 for the methyl protons along with multiplets for 10 aromatic protons at δ 7.56 - 7.90 and δ 7.93 - 8.23.



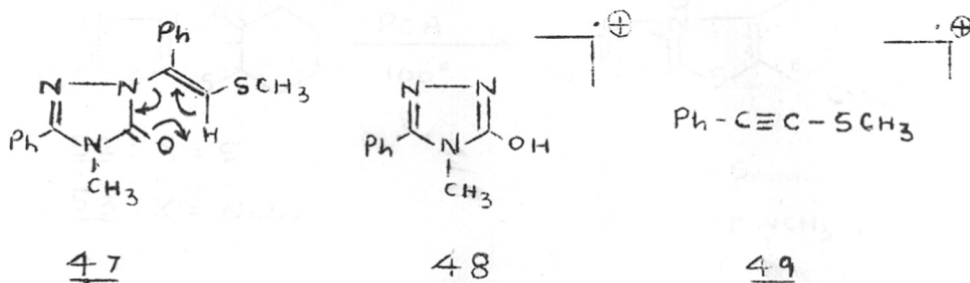
That, this compound has the structure 41 and not the alternative structure 46, was clear from the formation of 47 by its reaction with methanolic KCN. The compound 47 in its IR spectrum showed a sharp peak at 1700 cm^{-1} for a carbonyl group. The ^1H NMR exhibited a 3H singlet at δ 2.23 for the S-CH_3 protons, another 3H singlet at δ 3.30 for the N-CH_3 protons, a 1H singlet at δ 6.53 for the olefinic proton and a 10H multiplet at δ 7.0 - 7.7 for aromatic protons. Its mass



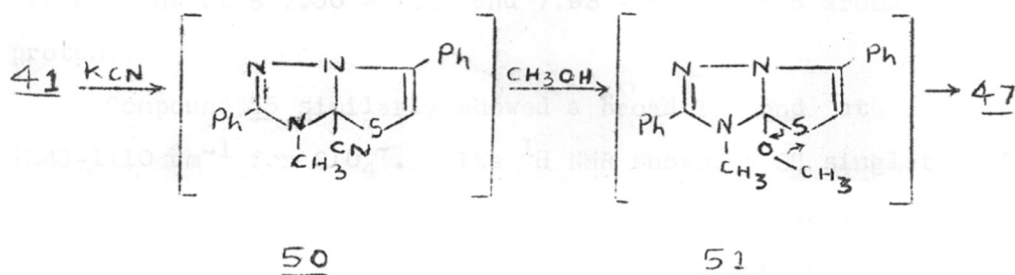
^1H NMR OF COMPOUND 41



Spectrum showed the expected M^+ ion at 323 along with the fragment ion at 276 $[\bar{M}^+ - S-CH_3]$. The structure 47 for the compound was further supported by the presence of fragment ions at 175 and 148 for 48 and 49 respectively.



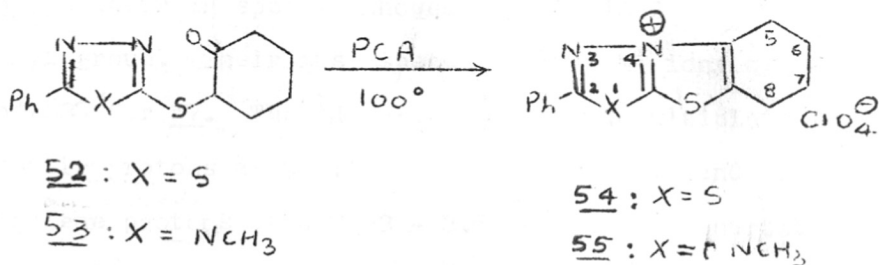
Compound 47, is expected to be formed by the rearrangement of 51 formed similar to 44.



Cyclodehydration of 2-[(2'-oxocyclohexyl)thio]-5-phenyl-1,3,4-thiadiazole and 4-methyl-5-[(2'-oxocyclohexyl)thio]-3-phenyl-1,2,4-triazole

Both 2-[(2'-oxocyclohexyl)thio]-5-phenyl-1,3,4-thiadiazole 52 and 4-methyl-5-[(2'-oxocyclohexyl)thio]-3-phenyl-1,2,4-triazole 53 were readily cyclodehydrated with PCA at 100° to 2-phenyl-5,6,7,8-tetrahydro-benzo (b) thiazolo [2,3-b] 1,3,4-thiadiazolium perchlorate 54 and 1-methyl-2-phenyl-5,6,7,8-

tetrahydro-benzo (b) thiazolo $\overline{3},2-b$ 1,2,4-triazolium perchlorate 55 respectively.



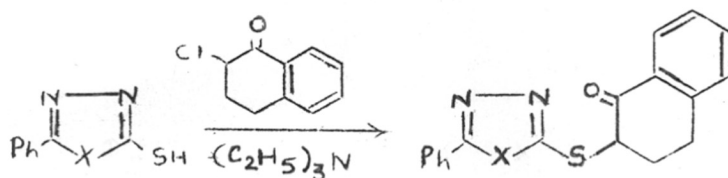
The perchlorate 54, in its IR spectrum showed bands at 1050-60 cm^{-1} and 1080-95 cm^{-1} for ClO_4^- . Its ^1H NMR exhibited multiplets at δ 2.06 - 2.40 and 2.93 - 3.40 for 8 methylenic protons and at δ 7.50 - 7.83 and 7.93 - 8.20 for 5 aromatic protons.

Compound 55 similarly showed a broad IR band at 1045-1110 cm^{-1} for ClO_4^- . Its ^1H NMR showed a 3H singlet at δ 4.10 for the methyl protons, 8H multiplets at δ 2.0 - 2.36 and 2.83 - 3.20 for the methylene protons and a 5H singlet at δ 7.7 for the aromatic protons.

Cyclodehydration of 5-phenyl-2- $\overline{2}$ '(3',4'-dihydro-1'(2'H)-naphthalenonyl)thio $\overline{7}$ -1,3,4-thiadiazole and 4-methyl-3-phenyl-5- $\overline{2}$ '(3',4'-dihydro-1'(2'H)-naphthalenonyl)thio $\overline{7}$ -1,2,4-triazole

5-Phenyl-2- $\overline{2}$ '(3',4'-dihydro-1'(2'H)-naphthalenonyl)thio $\overline{7}$ -1,3,4-thiadiazole 56 and 4-methyl-3-phenyl-5- $\overline{2}$ '(3',4'-dihydro-1'(2'H)-naphthalenonyl)thio $\overline{7}$ -1,2,4-triazole 57 were prepared by the action of 2-chloro-3,4-dihydro-1(2H)-naphthalenone

on 2-mercapto-5-phenyl-1,3,4-thiadiazole 58 (12) and 5-mercapto-4-methyl-3-phenyl-1,2,4-triazole 59 (13) respectively in refluxing benzene in presence of triethylamine. Both 56 and 57 in their IR spectra showed band at 1680 cm^{-1} for the carbonyl group. Their mass spectra showed M^+ ions at 338 for 56 and 335 for 57. The ^1H NMR of 56 showed multiplets for 9 aromatic protons at δ 7.1 - 7.6 and 7.8 - 8.2 and for 4 methylene protons at δ 2.33 - 3.50 and an ABX quartet for the methine proton centered at δ 5.10, while that of 57 exhibited a 3H singlet at δ 3.66 for the methyl protons, an ABX quartet for the methine proton centered at δ 4.60, a 4H multiplet at δ 2.0 - 3.33 for the methylene protons and a multiplet for 9 aromatic protons at δ 7.06 - 8.06.



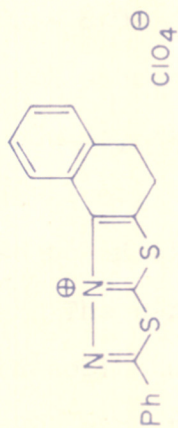
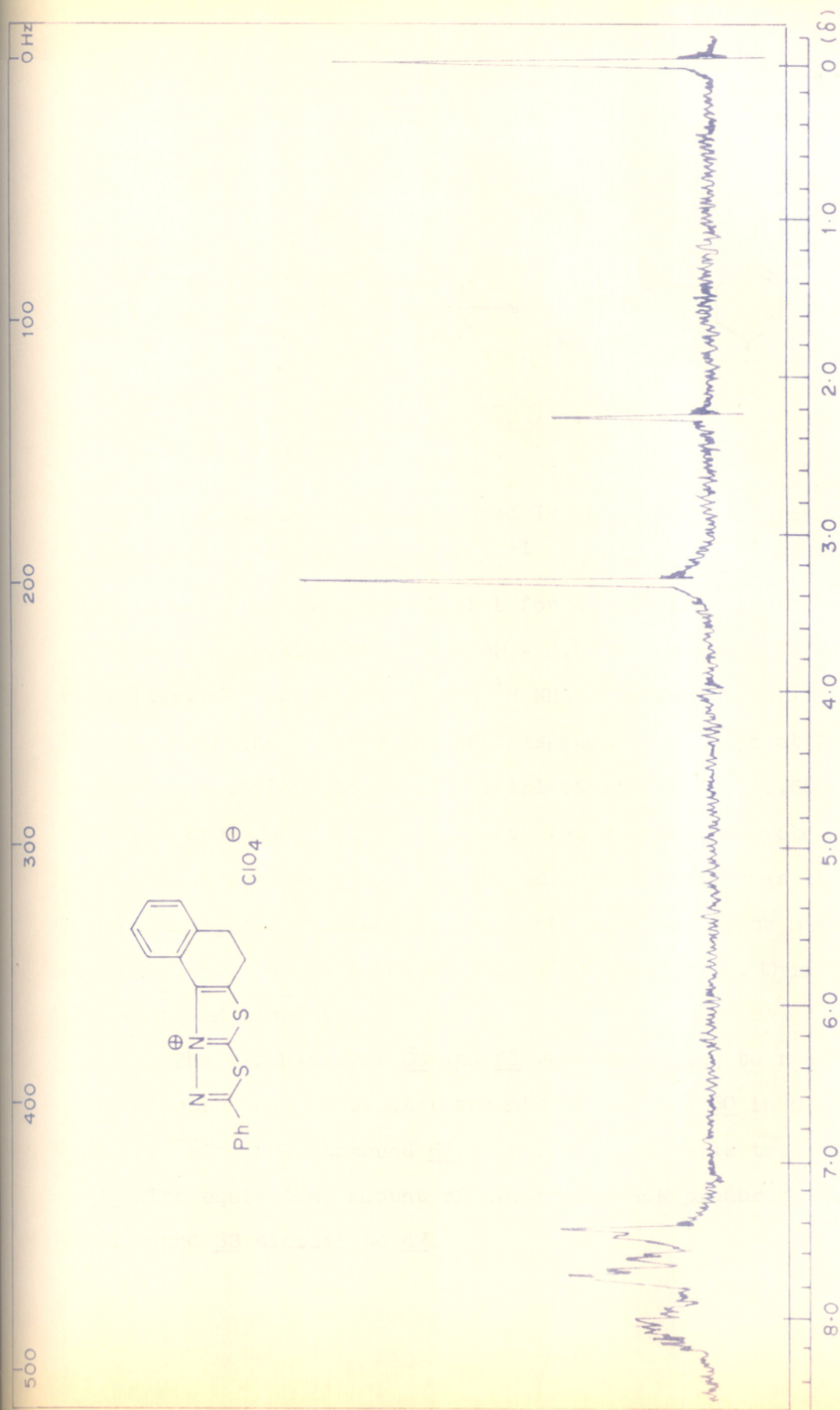
58 : $X = S$

56 : $X = S$

59 : $X = \text{NCH}_3$

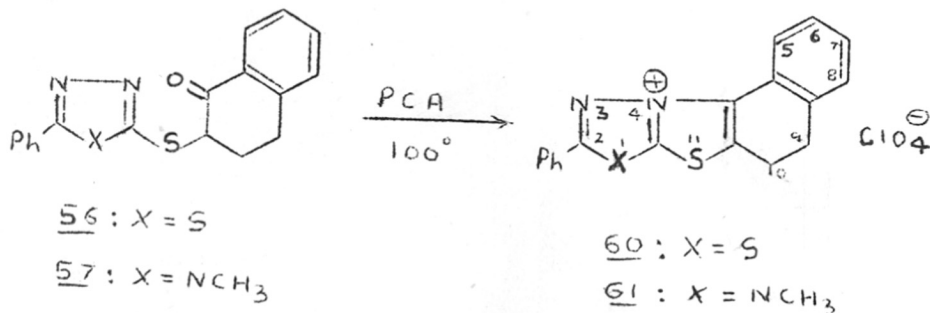
57 : $X = \text{NCH}_3$

Compounds 56 and 57, on treatment with PCA at 100° were cyclodehydrated to 9,10-dihydro-2-phenyl- $\overline{\text{naphtho}}(1,2\text{-d})$ thiazolo $\overline{[2,3\text{-b}]}$ 1,3,4-thiadiazolium perchlorate 60 and 9,10-dihydro-1-methyl-2-phenyl- $\overline{\text{naphtho}}(1,2\text{-d})$ thiazolo $\overline{[3,2\text{-b}]}$ 1,2,4-triazolium perchlorate 61 respectively.



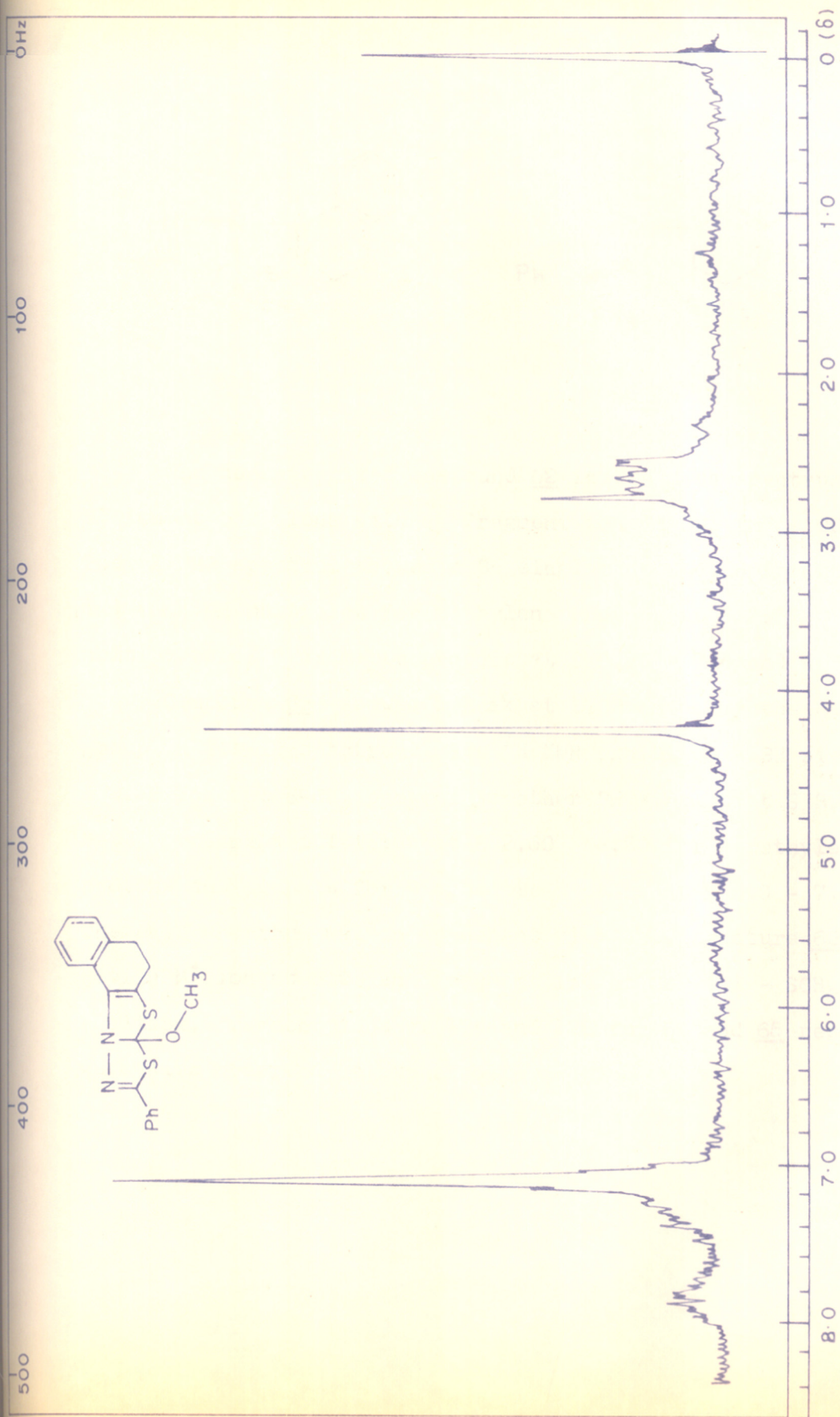
106

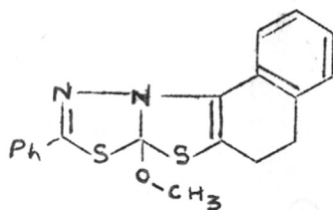
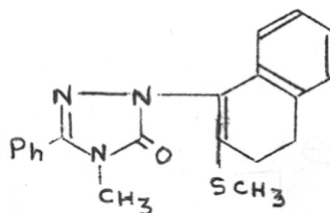
^1H NMR OF COMPOUND 60



Compounds 60 and 61 showed IR bands for perchlorate at 1040-1095 cm^{-1} and 1050-1110 cm^{-1} respectively. The ^1H NMR spectrum of 60 showed a singlet for 4 methylene protons at δ 3.36 and multiplets at δ 7.33 - 8.23 for 9 aromatic protons. Similarly 61 exhibited in its ^1H NMR spectrum a singlet at δ 3.33 for the 4 methylene protons, another singlet at δ 4.20 for the methyl protons and multiplets at δ 7.40 - 7.60, 7.80 - 8.03 and δ 8.30 - 8.70 for the 9 aromatic protons. The ^1H NMR spectra of 60 and 61 are quite interesting as in both the compounds, all the 4-methylene protons appear to be magnetically equivalent, and so do not couple with each other, thus giving rise to 4H singlets.

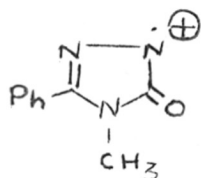
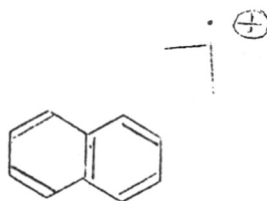
The perchlorates 60 and 61 were subjected to reaction with methanolic KCN. Equimolar amounts of KCN and 60 in methanol at 70° gave the compound 62 similar to 44 while treatment of 61 with equivalent amount of methanolic KCN produced the compound 63 similar to 47.



6263

The dequaternized compound 62 in its mass spectrum showed M^+ ion at 352 along with a fragment ion at 321 ($M^+ - OCH_3$). The 1H NMR spectrum showed a 3H singlet at δ 4.26 for the methyl protons, a 4H multiplet for methylene protons at δ 2.53 - 2.96 and multiplets for 9 aromatic protons at δ 6.96 - 7.4 and δ 7.63 - 8.0.

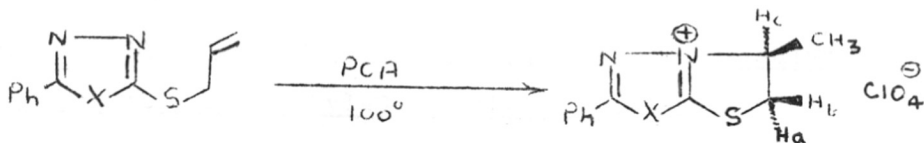
Compound 63 showed a peak at 1700 cm^{-1} for the carbonyl group in its IR spectrum. Its 1H NMR exhibited a 3H singlet at δ 2.26 for the S- CH_3 protons, another 3H singlet at δ 3.46 for N- CH_3 protons, a multiplet at δ 2.50 - 3.20 for 4 methylene protons and signals for 9 aromatic protons at δ 6.9 - 7.73. The mass spectrum was in agreement with the structure 63 giving M^+ ion at 349, and fragment ion at 302 ($M^+ - SCH_3$). In addition, fragment ions at 174 and 128 for 64 and 65 respectively were also observed as expected.

6465

Compounds 62 and 63 must have been formed similar to 44 and 47 respectively.

Cyclization of 2-allylthio-5-phenyl-1,3,4-thiadiazole and 5-allylthio-4-methyl-3-phenyl-1,2,4-triazole

Both 2-allylthio-5-phenyl-1,3,4-thiadiazole 66 and 5-allylthio-4-methyl-3-phenyl-1,2,4-triazole 67 were easily cyclized with PCA at 100° to produce 5,6-dihydro-5-methyl-2-phenyl-thiazolo[2,3-b]1,3,4-thiadiazolium perchlorate 68 and 5,6-dihydro-1,5-dimethyl-2-phenyl-thiazolo [3,2-b]1,2,4-triazolium perchlorate 69 respectively.

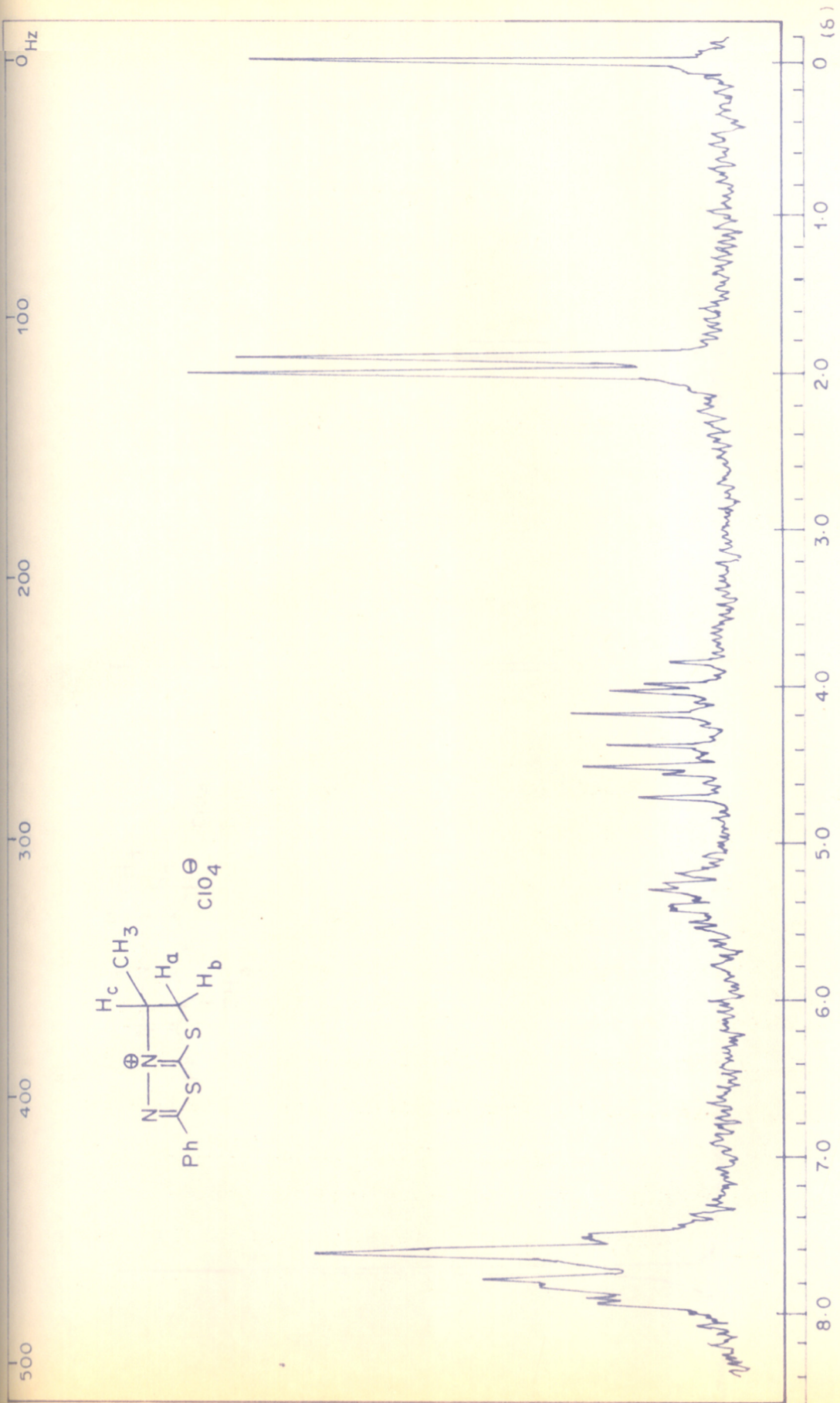
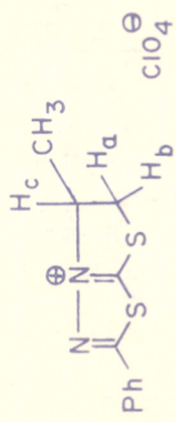
66: X = S68: X = S67: X = NCH₃69: X = NCH₃

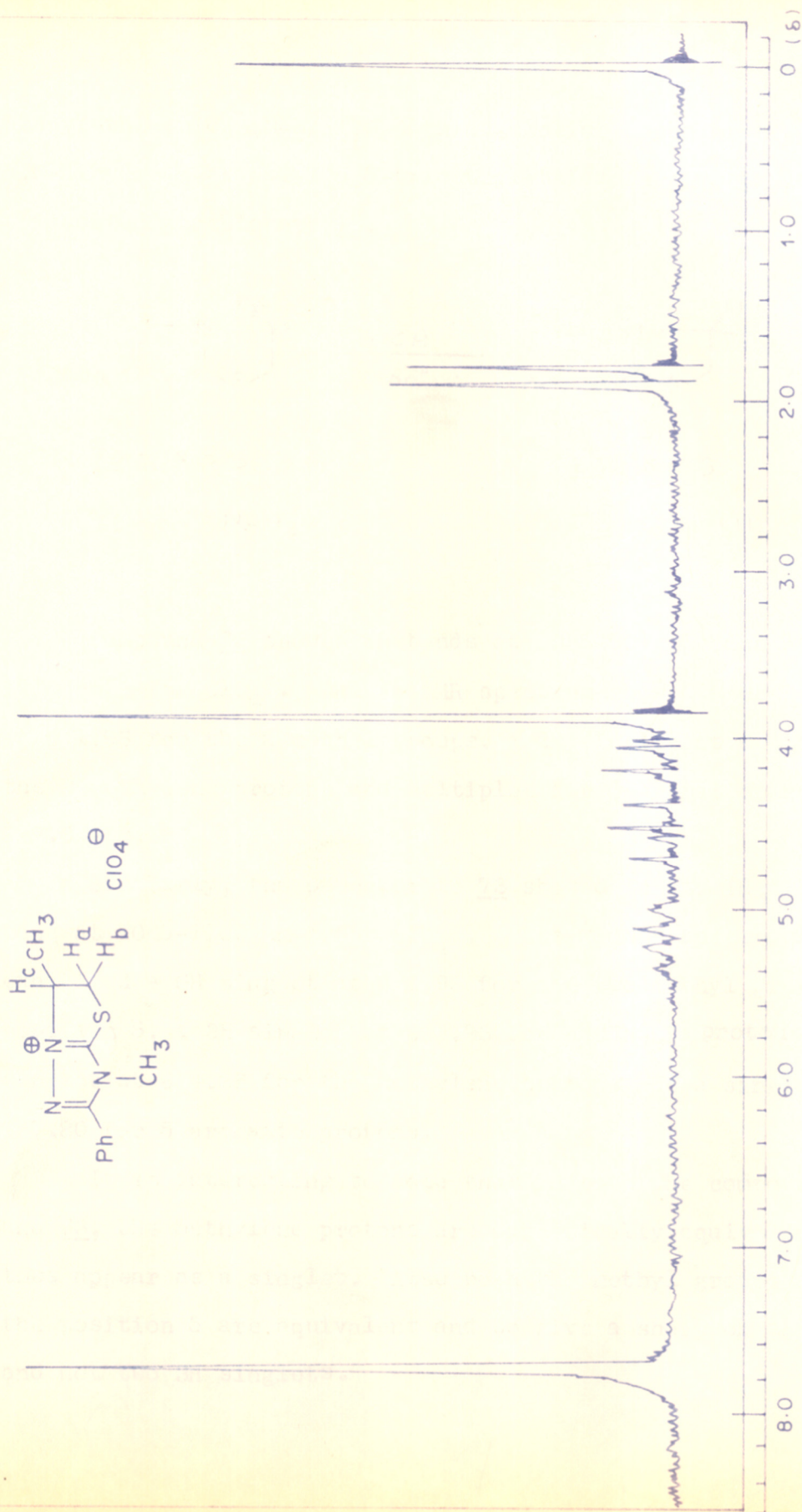
The cyclized perchlorate 68 showed a broad band in IR at $1055-1110\text{ cm}^{-1}$ for ClO_4^- . In the ^1H NMR spectrum, it showed a 3H doublet at δ 1.96 ($J = 7\text{ Hz}$) for the methyl protons, a 1H multiplet centered at δ 5.33 for the methine proton H_c , a multiplet for 5 aromatic protons at δ 7.33 - 8.03, a 1H doublet of doublet at δ 4.5 ($J = 8$ and 12 Hz) for the proton H_b trans to H_c and another 1H doublet of doublet at δ 4.0 ($J = 10$ and 12 Hz) for the proton H_a cis to H_c . Thus it appears that the geminal coupling constant for $\text{H}_a - \text{H}_b$ is 12 Hz while the vicinal coupling constants for $\text{H}_b - \text{H}_c$ (trans) is 8 Hz and $\text{H}_a - \text{H}_c$ (cis) is 10 Hz .

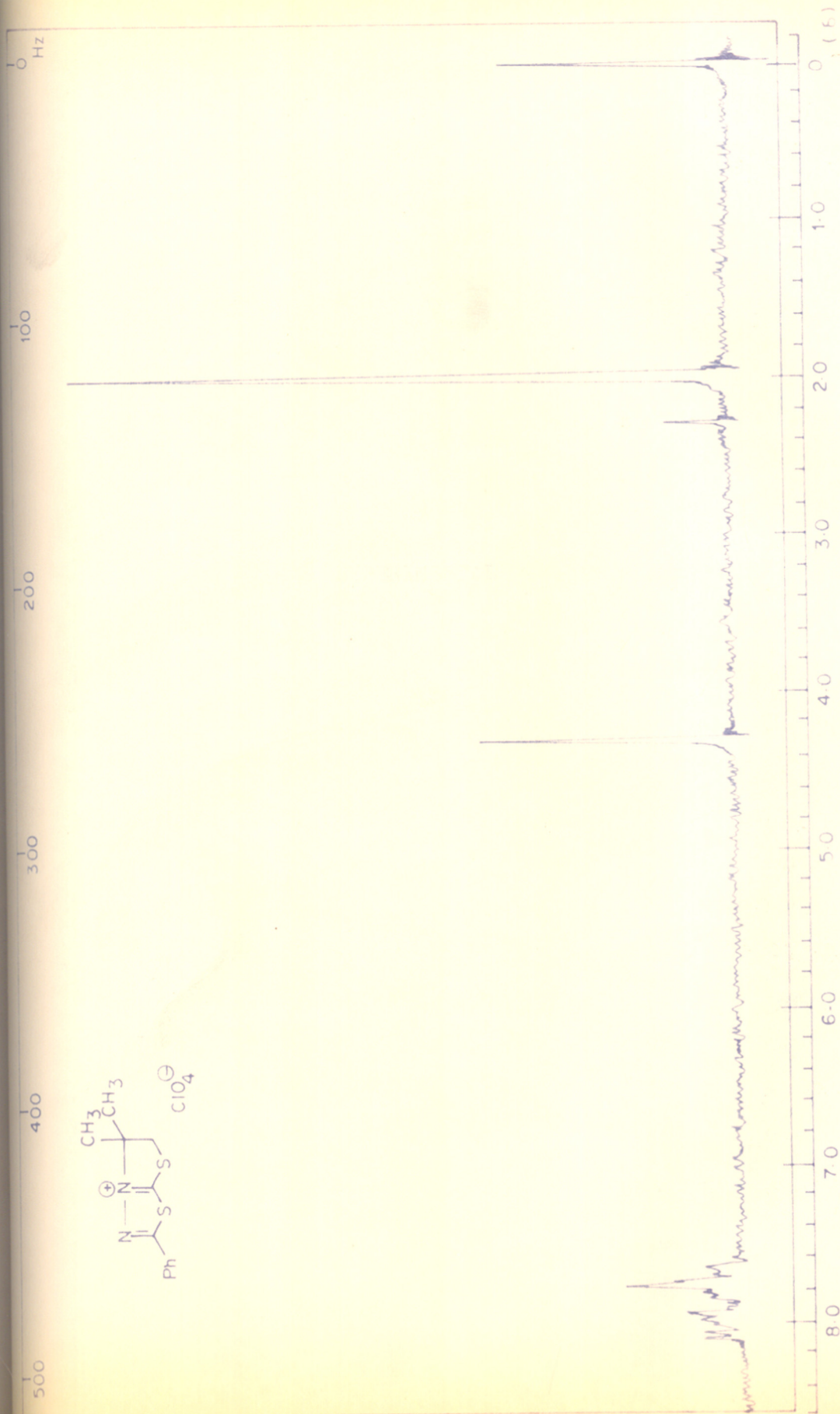
The compound 69 similarly showed in IR a broad band at $1055-1085\text{ cm}^{-1}$ for ClO_4^- . Its ^1H NMR exhibited a 3H doublet at δ 1.86 ($J = 7\text{ Hz}$) for the methyl protons at position 5, a 3H singlet at δ 3.90 for the N-CH_3 protons, a 1H doublet of doublet at δ 4.03 ($J = 8$ and 12 Hz) for one of the methylene protons H_a , another 1H doublet of doublet at δ 4.53 ($J = 8$ and 12 Hz) for the other methylene proton H_b , a 1H multiplet at δ 5.2 for the methine proton and a singlet at δ 7.76 for the 5 aromatic protons. It thus appears that the geminal coupling constant for $\text{H}_a - \text{H}_b$ is 12 Hz while the vicinal coupling constant for $\text{H}_a - \text{H}_c$ and $\text{H}_b - \text{H}_c$ is 8 Hz .

Cyclization of 2-methallylthio-5-phenyl-1,3,4-thiadiazole and 5-methallylthio-4-methyl-3-phenyl-1,2,4-triazole

Both 2-methallylthio-5-phenyl-1,3,4-thiadiazole 70 and 5-methallylthio-4-methyl-3-phenyl-1,2,4-triazole 71 were easily cyclized with PCA at 100° to form 5,6-dihydro-5,5-dimethyl-2-





^1H NMR OF COMPOUND 72

EXPERIMENTAL for

Reaction of 2-phenacylthio-5-phenyl-1,3,4-oxadiazole 37 with PCA

(a) At 100°

Compound 37 (0.300 g, 0.001 M) was treated with PCA (70%) (3 ml) and the mixture was heated on water bath for 15 hr. Then the reaction mixture was diluted with water. The solid which separated out was filtered and washed with water.

This solid gave superimposable IR spectrum and undepressed mixed m.p. with the starting compound 37.

(b) At 140°

A mixture of compound 37 (0.300 g; 0.001 M) and PCA (3 ml) was heated in an oil bath at 140° for 4 hr. Dilution of this reaction mixture with water gave a reddish black solid. This was, however, observed to be a complex mixture (TLC) which could not be separated either by chromatography or by crystallization.

Reaction of 2-phenacylthio-5-phenyl-1,3,4-thiadiazole 38 with PCA

Compound 38 (0.100 g; 0.0003 M) was taken in PCA (1 ml) and the mixture was heated on water bath for 1 hr. After cooling, methanol was added to the reaction mixture when a white solid separated out. The solid was filtered, washed with water and crystallized from methanol + chloroform (1:1) into fine needles of 40 (0.09 g; 70%).

Compound 40: m.p. 245°

Elemental analyses: Found, C: 48.51%; H: 2.93%; N: 7.14%;

$C_{16}H_{11}ClN_2O_4S_2$ requires, C: 48.67%;

H: 2.78%; N: 7.10%.

UV (Methanol): $\lambda_{\max}$ 272 nm ($\log \epsilon$ 4.77); $\lambda_{\max}$ 209 nm
($\log \epsilon$ 4.91).

IR ($\nu_{\max}^{\text{nujol}}$): 1600 (C = N); 1050-1110 (ClO_4^-)

^1H NMR (TFA): 7.53 - 8.20 (m, 11H, aromatic).

Reaction of 4-methyl-5-phenacylthio-3-phenyl-1,2,4-triazole 39 with PCA

A mixture of compound 39 (0.100 g; 0.0003 M) and PCA (1 ml) was heated on water bath for 30 minutes. The solution became clear. This was cooled and methanol was added when a solid separated out. It was filtered and recrystallized from aqueous methanol into fine needles of 41 (0.110 g; 85%).

Compound 41 : m.p. 214°.

Elemental analyses: Found, C: 52.34%; H: 3.44%; N: 10.81%.

$\text{C}_{17}\text{H}_{14}\text{ClN}_3\text{O}_4\text{S}$ requires, C: 52.11%; H: 3.58%;
N: 10.73%.

U.V. (Methanol): $\lambda_{\max}$ 211 nm ($\log \epsilon$ 4.45); $\lambda_{\max}$ 242 nm
($\log \epsilon$ 4.38).

IR ($\nu_{\max}^{\text{nujol}}$): 1060-1110 (ClO_4^-)

^1H NMR (TFA): 4.23 (s, 3H, methyl), 7.56 - 7.90 (m, 9H) and
7.93 - 8.23 (m, 2 H) (aromatic).

Reaction of 40 with methanolic KCN

To a mixture of compound 40 (0.200 g; 0.0005 M) and KCN (0.033 g; 0.0005 M), 3-4 drops of water was added. Then methanol was added till a clear solution was obtained. This was heated at 70° for 2 hr. The reaction mixture was then

extracted with chloroform (2 x 50 ml). The chloroform extract was washed with 10% sodium carbonate solution and then with water. It was then dried (Na_2SO_4). The residue obtained after evaporation of chloroform was then chromatographed over silica gel (1:20). Elution with benzene + ethylacetate (19:1) gave the compound 44 (0.090 g; 55%).

Compound 44: m.p. 94° .

Elemental analyses: Found, C: 62.71%; H: 4.09%; N: 8.80%.

$\text{C}_{17}\text{H}_{14}\text{N}_2\text{OS}_2$ requires, C: 62.57%; H: 4.29%;
N: 8.59%.

IR ($\nu_{\text{max}}^{\text{chloroform}}$): 1590 and 1600 (C = N)

^1H NMR (CCl_4): 4.15 (s, 3H, methyl); 6.30 (s, 1H, olefinic);
7.00 - 7.60 (m, 10H, aromatic)

Mass : 326 (M^+ ion).

Reaction of 41 with methanolic KCN

A clear solution of compound 41 (0.200 g; 0.0005 M), KCN (0.033 g; 0.0005 M), 3-4 drops of water and sufficient methanol was heated at 70° for 2 hr. Then a similar work out as above gave the compound 47 (0.115 g; 70%).

Compound 47: m.p. 118°

Elemental analyses: Found, C: 66.98%; H: 5.60%; N: 12.80%.

$\text{C}_{18}\text{H}_{17}\text{N}_3\text{OS}$ requires, C: 66.87%; H: 5.26%;
N: 13.00%.

IR ($\nu_{\text{max}}^{\text{nujol}}$): 1600 (C = N); 1700 (C = O).

^1H NMR (CCl_4): 2.23 (s, 3H, S- CH_3 protons); 3.30 (s, 3H, N- CH_3 protons); 6.53 (s, 1H, olefinic);
7.00 - 7.7 (m, 10H, aromatic).

Mass: 323 (M^+ ion).

Reaction of 2-[(2'-oxocyclohexyl)thio]-5-phenyl-1,3,4-thiadiazole 52 with PCA

Compound 52 (0.200 g; 0.0006 M) was treated with PCA (2 ml) and heated on water bath for 15 minutes. The starting compound 52 went into solution after 2 minutes and again a solid appeared after 5 minutes. Methanol was then added. The solid was filtered and washed with water. It was recrystallized from chloroform + methanol (1:1) into fine needles of 54 (0.200 g; 77%).

Compound 54: m.p. 284°.

Elemental analyses: Found, C: 44.83%; H: 3.67%; N: 7.30%.

$C_{14}H_{13}ClN_2O_4S_2$ requires, C: 45.10%;

H: 3.49%; N: 7.52%.

UV (Methanol): λ_{max} 211.5 nm (log ϵ 4.00); λ_{max} 272 nm (log ϵ 4.25).

IR (ν_{max}^{nujol}): 1050-1060 (ClO_4^-).

1H NMR (TFA): 2.06 - 2.40 (m, 4H) and 2.93 - 3.40 (m, 4H) (methylene protons); 7.50 - 7.83 (m, 3H) and 7.93 - 8.20 (m, 2H) (aromatic).

Reaction of 4-methyl-5-[(2'-oxocyclohexyl)thio]-3-phenyl-1,2,4-triazole 53 with PCA

Compound 53 (0.250 g; 0.0008 M) and PCA (2.5 ml) were mixed and heated on a water bath for 15 min. The solution was then cooled and methanol added when a solid was thrown out. It was filtered and washed with water. It was then crystallized from aqueous methanol into colourless crystals of 55 (0.150 g; 47%).

Compound 55 : m.p. 186°.

Elemental analyses: Found, C: 48.53%; H: 4.62%; N: 11.44%.

$C_{15}H_{16}ClN_3O_4S$ requires, C: 48.71%; H: 4.33%;
N: 11.36%.

UV (Methanol): λ_{max} 207.5 nm (log ϵ 4.15); λ_{max} 234 nm (log ϵ 4.16)

IR (ν_{max}^{nujol}): 1045 - 1110 (ClO_4^-).

1H NMR (TFA): 2.0 - 2.36 (m, 4H) and 2.83 - 3.20 (m, 4H)

(methylene protons); 4.10 (s, 3H, methyl); 7.70

(s, 5H, aromatic).

Preparation of 5-phenyl-2-(2'-(3',4'-dihydro-1'(2H)-naphthalenonyl)thio)-1,3,4-thiadiazole 56

A mixture of compound 58 (0.970 g; 0.005 M), 2-chloro-3,4-dihydro-1(2H)-naphthalenone (0.900 g; 0.005 M) and triethylamine (0.505 g; 0.005 M) was refluxed in benzene (20 ml) for 3 hr. The reaction mixture was then washed successively with water, 10% sodium hydroxide solution and again with water and finally dried (Na_2SO_4). The residue obtained after evaporation of benzene was then crystallized from pet. ether + benzene (1:1) into colourless crystals of 56 (1.25 g; 75%).

Compound 56 : m.p. 138°.

Elemental analyses: Found, C: 64.17%; H: 4.39%; N: 8.51%.

$C_{18}H_{14}N_2OS_2$ requires, C: 63.90%; H: 4.14%;
N: 8.28%.

IR (ν_{max}^{nujol}): 1600 (C = N); 1680 (C = O).

1H NMR (CCl_4): 2.33 - 3.50 (m, 4H, methylene protons);

5.10 (ABX quartet, 1H, methine); 7.10 - 7.60 (m, 7H)

and 7.80 - 8.20 (m, 2H) (aromatic).

Mass : 338 (M^+ ion).

Preparation of 4-methyl-3-phenyl-5-[2'-(3',4'-dihydro-1'-(2'H)-naphthalenonyl)thio]-1,2,4-triazole 57

A mixture of compound 59 (0.955 g; 0.005 M), 2-chloro-3,4-dihydro-1(2H)-naphthalenone (0.900 g, 0.005 M) and triethylamine (0.505 g; 0.005 M) was refluxed in benzene (20 ml) for 3 hr. The reaction mixture was then successively washed with water, 10% sodium hydroxide solution and again with water. It was then dried (Na_2SO_4). The residue obtained by evaporation of solvent was passed through a silica gel (1:20) column. The compound 57 came in benzene + ethyl acetate (9:1). It was obtained as a colourless oil (0.670 g; 40%).

Compound 57:

Elemental analyses: Found, C: 68.18%; H: 4.83%; N: 12.60%.

$\text{C}_{19}\text{H}_{17}\text{N}_3\text{OS}$ requires, C: 68.06%; H: 5.07%;
N: 12.54%.

IR ($\nu_{\text{max}}^{\text{liq.film}}$): 1680 (C = O).

^1H NMR (CCl_4): 2.00 - 3.33 (m, 4H, methylene); 3.66 (s, 3H, methyl);
4.60 (ABX quartet, J = 5 and 11 Hz; 1 H, methine);
7.06 - 8.06 (m, 9H, aromatic).

Mass: 335 (M^+ ion).

Reaction of 56 with PCA

Compound 56 (0.150 g; 0.0004 M) was treated with PCA (1.5 ml) and the mixture was heated on water bath for 15 minutes. It was then cooled and then little methanol was added. This was diluted with water when a solid separated out. It was filtered, washed with water and then crystallized from aqueous methanol into

colourless crystals of 60 (0.130 g; 70%).

Compound 60: m.p. 243°

Elemental analyses: Found, C: 51.20%; H: 3.36%; N: 6.48%.

$C_{18}H_{13}ClN_2O_4S_2$ requires, C: 51.37%;

H: 3.09%; N: 6.66%.

UV (Methanol): λ_{max} 212 nm (log ϵ 4.44); λ_{max} 285 nm
(log ϵ 4.38).

IR (ν_{max}^{nujol}): 1040-1095 (ClO_4^-).

1H NMR (TFA): 3.36 (s, 4H, methylene protons); 7.33 - 8.23
(m, 9H, aromatic).

Reaction of 57 with PCA

A mixture of compound 57 (0.200 g; 0.0006 M) and PCA (2 ml) was heated on a water bath for 20 minutes. Initially clear solution suddenly solidified. To this solid mass, methanol and water were added and filtered. The solid was crystallized from aqueous methanol into needles of 61 (0.200 g; 80%).

Compound 61: m.p. 249°.

Elemental analyses: Found, C: 54.92%; H: 4.04%; N: 9.85%.

$C_{19}H_{16}ClN_3O_4S$ requires, C: 54.61%;

H: 3.83%; N: 10.06%.

UV (Methanol): λ_{max} 209 nm (log ϵ 4.52); λ_{max} 273 nm (log ϵ 4.23)

IR (ν_{max}^{nujol}): 1040-1095 (ClO_4^-).

1H NMR (TFA) : 3.33 (s, 4H, methylene protons); 4.20 (s, 3H, methyl); 7.40 - 7.60, 7.80 - 8.03 and 8.30 - 8.70
(m, 9H, aromatic).

Reaction of 60 with methanolic KCN

To a mixture of compound 60 (0.150 g; 0.00035 M), KCN (0.023 g; 0.00035 M) and 3-4 drops of water, methanol was added to make a clear solution. It was then heated at 70° for 2 hr. The reaction mixture was then extracted with chloroform (2 x 50 ml). The chloroform extract was washed successively with 10% sodium carbonate solution and water. It was then dried (Na₂SO₄) and the solvent evaporated. The residue was chromatographed (silica gel, 1:20). The compound 62 came in benzene + ethyl acetate (9:1) (0.075 g; 60%).

Compound 62: m.p. 128°

Elemental analyses: Found, C: 64.56%; H: 4.32%; N: 8.13%.

C₁₉H₁₆N₂OS₂ requires, C: 64.77%; H: 4.54%;
N: 7.95%.

IR (ν_{max} ^{chloroform}): 1590 (phenyl); 1610 (C = N).

¹H NMR (CCl₄): 2.53 - 2.96 (m, 4H, methylene protons);
4.26 (s, 3H, methyl); 6.96 - 7.4 (m, 7H) and
7.63 - 8.00 (m, 2H) (aromatic).

Mass: 352 (M⁺ ion).

Reaction of 61 with PCA

A clear solution of compound 61 (0.200 g; 0.00048 M), KCN (0.021 g; 0.00048 M), 3-4 drops of water and sufficient methanol was heated at 70° for 2 hr. Then a similar workout as above gave the compound 63 (0.130 g; 80%).

Compound 63: m.p. 146°

Elemental analyses: Found, C: 69.01%; H: 5.46%; N: 12.31%.

$C_{20}H_{19}N_3OS$ requires, C: 68.77%; H: 5.44%;
N: 12.03%.

IR ($\nu_{\max}^{\text{nujol}}$): 1600 (C = N); 1700 (C = O).

1H NMR (CCl_4): 2.26 (s, 3H, S-CH₃ protons); 2.50 - 3.20 (m, 4H, methylene protons), 3.46 (s, 3H, N-CH₃ protons); 6.96 - 7.4 and 7.63 - 8.0 (m, 9H, aromatic).

Mass: 349 (M^+ ion)

Reaction of 2-allylthio-5-phenyl-1,3,4-thiadiazole 66 with PCA

Compound 66 (0.150 g; 0.00064 M) was heated with PCA (1.5 ml) on a water bath for 2 hr. After cooling the reaction mixture, little methanol and excess of water were added. The solid which separated out was filtered and washed with water. It was crystallized with aqueous methanol into colourless crystals of 68 (0.160 g; 75%).

Compound 68: m.p. 168°.

Elemental analyses: Found, C: 39.33%; H: 3.42%; N: 8.14%.

$C_{11}H_{11}ClN_2O_4S_2$ requires, C: 39.46%;
H: 3.29%; N: 8.37%.

UV (Methanol): $\lambda_{\max}$ 208 nm (log ϵ 4.27); $\lambda_{\max}$ 318 nm (log ϵ 4.16).

IR ($\nu_{\max}^{\text{nujol}}$): 1055 - 1110 (ClO_4^-)

1H NMR (TFA): 1.96 (d, J = 7 Hz; 3H, methyl); 4.0 (dd, J = 10 and 12 Hz; 1H, H_a); 4.50 (dd, J = 8 and 12 Hz; 1H, H_b); 5.33 (m, 1H, H_c); 7.33 - 8.03 (m, 5H, aromatic).

Reaction of 5-allylthio-4-methyl-3-phenyl-1,2,4-triazole
67 with PCA

The compound 67 (0.250 g; 0.0011 M) was mixed with PCA (2.5 ml) and the mixture was heated on a water bath for 2 hr. After cooling this reaction mixture, little methanol and excess of water were added. This was cooled to 0° overnight when a solid separated out. It was filtered and recrystallized from aqueous methanol to give compound 69 (0.250 g; 70%).

Compound 69 : m.p. 138°.

Elemental analyses: Found, C: 43.56%; H: 4.33%; N: 12.80%.

$C_{12}H_{14}ClN_3O_4S$ requires, C: 43.44%;

H: 4.22%; N: 12.67%.

UV (Methanol): λ_{max} 210 nm (log ϵ 4.023); λ_{max} 249.5 nm (log ϵ 4.12).

IR (ν_{max}^{nujol}): 1055 - 1085 (ClO_4^-)

1H NMR (TFA): 1.86 (d, J = 7 Hz; 3H, methyl at position 5);
 3.90 (s, 3H, N - CH₃ protons); 4.03 (dd, J = 8 and
 12 Hz; 1H, H_a); 4.53 (dd, J = 8 and 12 Hz;
 1H, H_b); 5.20 (m, 1H, H_c); 7.76 (s, 5H, aromatic).

Reaction of 2-methallylthio-5-phenyl-1,3,4-thiadiazole
70 with PCA

Compound 70 (0.200 g; 0.0008 M) was heated with PCA (2 ml) at 100° for 1 hr. After cooling the reaction mixture, little methanol and a large excess of water were added. A solid which separated out was filtered. It was crystallized from aqueous methanol to irregular crystals of 72 (0.155 g; 55%).

Compound 72 : m.p. 197°.

Elemental analyses: Found, C: 41.11%; H: 3.92%; N: 8.16%.

$C_{12}H_{13}ClN_2O_4S_2$ requires, C: 41.32%;
H: 3.73%; N: 8.03%.

UV (Methanol): λ_{max} 210.5 nm (log ϵ 4.24); λ_{max} 318 nm
(log ϵ 4.19).

IR (ν_{max}^{nujol}): 1035-1050 and 1065-1110 (ClO_4^-).

1H NMR (TFA): 1.96 (s, 6H, 2-methyl groups at position 5);
4.30 (s, 2H, methylene protons); 7.60 - 8.16
(m, 5H, aromatic).

Reaction of 5-methylallylthio-4-methyl-3-phenyl-1,2,4-triazole
71 with PCA

The compound 71 (0.200 g; 0.0008 M) was heated with
PCA (2 ml) on a water bath for 2 hr. After cooling the reaction
mixture, little methanol and excess of water were added to it.
This was cooled at 0° for 8-10 hr. when the crystals of 73
separated out. It was washed with cold water.

Yield: (0.070 g; 25%). m.p. 143°.

Elemental analyses: Found, C: 44.86%; H: 4.50%; N: 12.30%.

$C_{13}H_{16}ClN_3O_4S$ requires, C: 45.15%;
H: 4.63%; N: 12.16%.

UV (Methanol): λ_{max} 208 nm (log ϵ 4.07); λ_{max} 249 nm.
(log ϵ 4.14).

IR (ν_{max}^{nujol}): 1045 - 1110 (ClO_4^-)

1H NMR (TFA): 1.93 (s, 6H, 2-methyl groups at position 5);
3.93 (s, 3H, N-CH₃ protons); 4.26 (s, 2H,
methylene); 7.80 (s, 5H, aromatic).

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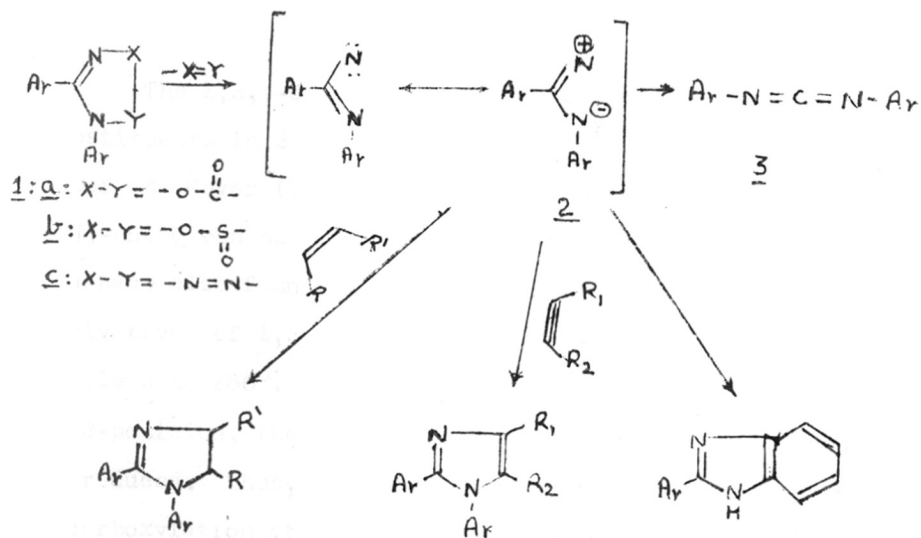
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CHAPTER IV

THERMAL REARRANGEMENT OF 1,3,4- OXADIAZOLE DERIVATIVES*

INTRODUCTION

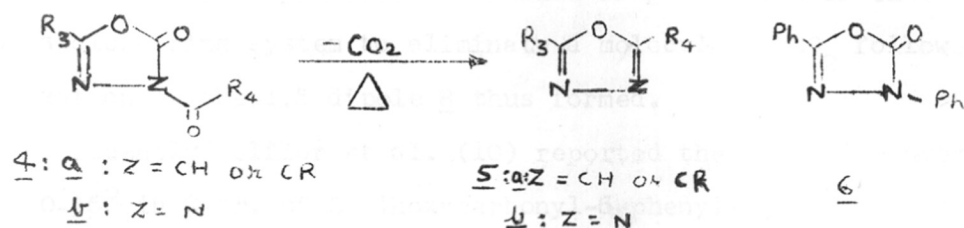
Many heterocyclic systems incorporating the groupings $-O-\overset{\overset{O}{\parallel}}{C}-$, $-O-\overset{\overset{O}{\parallel}}{S}-$, $-N=N-$ in their ring structures are known to eliminate CO_2 , SO_2 , N_2 respectively at elevated temperatures by thermal cleavage of the ring system. Thus 1,2,4-oxadiazol-5-ones 1a (1), 1,2,3,5-oxathiadiazol-2-ones 1b (2) and tetrazoles 1c (3,4) are thermally unstable, and decompose when heated, extruding a molecule of CO_2 , SO_2 and N_2 respectively, and forming the 1,3 dipoles 2. These dipoles are known to dimerize (5) or cyclize through the isomeric 1,5 dipoles or rearrange to the carbodiimides 3. These 1,3 dipoles can also be trapped with the usual olefinic or acetylenic dipolarophiles (5).



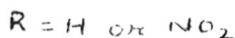
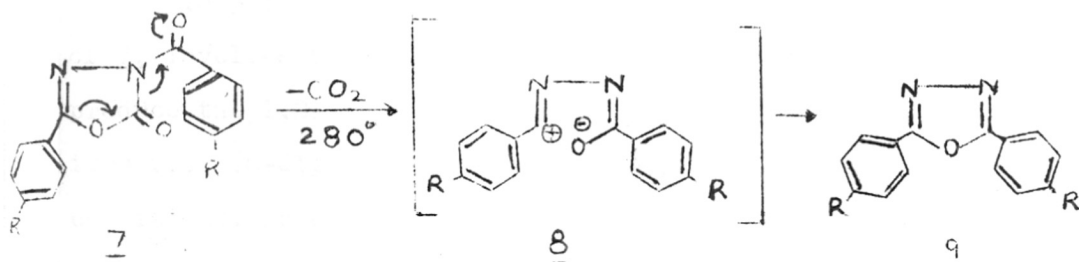
The temperature required for thermal decomposition of these heterocycles depends on the ring system concerned and the various substituents attached to it. Thus compounds with

structure 1a are decarboxylated only above 220° ; compounds 1b lose SO_2 even at $80-100^{\circ}$ while structures 1c eliminate N_2 only at $180-200^{\circ}$ (1-4).

Oxazol-5-ones 4a (6) and 1,3,4-oxadiazol-2-ones 4b are also known to decarboxylate thermally into the corresponding 2,5 disubstituted oxazoles and 1,3,4-oxadiazoles respectively.

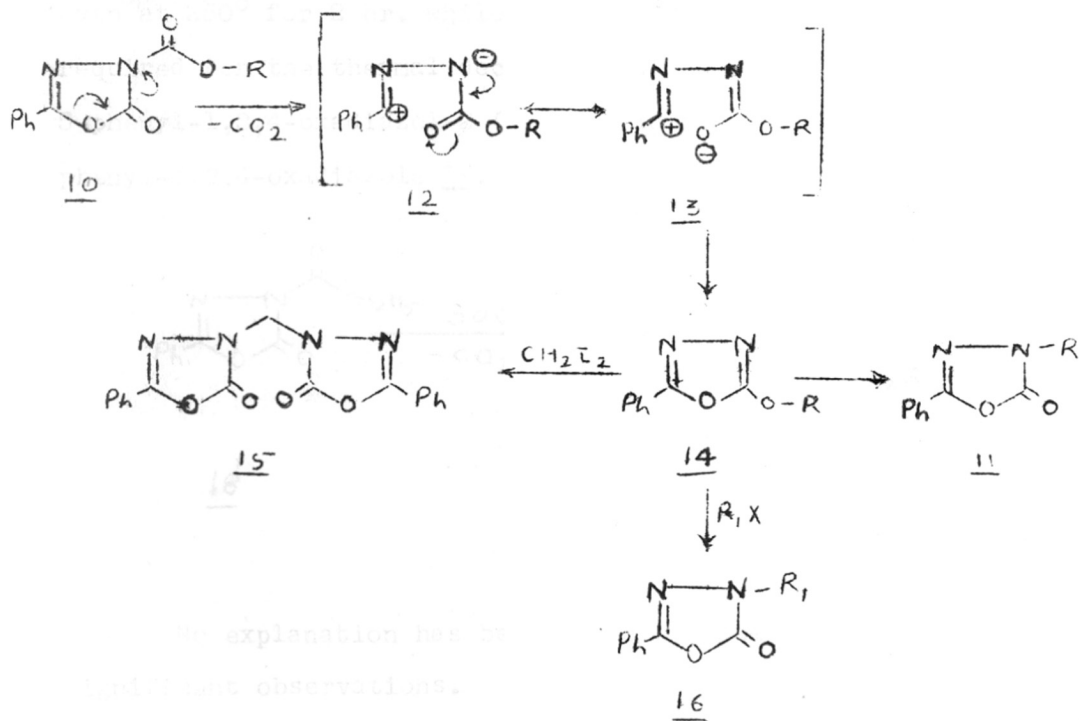


The 1,3,4-oxadiazol-2(3H)-ones with alkyl or aryl substituents in 3 and 5 positions are thermally quite stable. Sauer and Meyer (7) reported that 3,5-diphenyl-1,3,4-oxadiazol-2(3H)-one 6 can be distilled unchanged at 300° . Reimlinger et al. (8) have also found several 3,5-disubstituted alkyl/aryl derivatives of 1,3,4-oxadiazol-2(3H)-ones to be thermally stable upto 250° . However, with an acyl or similar substituent in 3-position, the thermal stability of oxadiazolone ring system is reduced. Thus, Stolle and Krauch (9) reported the thermal decarboxylation at 280° of 3-aryl-5-aryl-1,3,4-oxadiazol-2(3H)-ones 7 to give 2,5-diaryl-1,3,4-oxadiazoles 9.



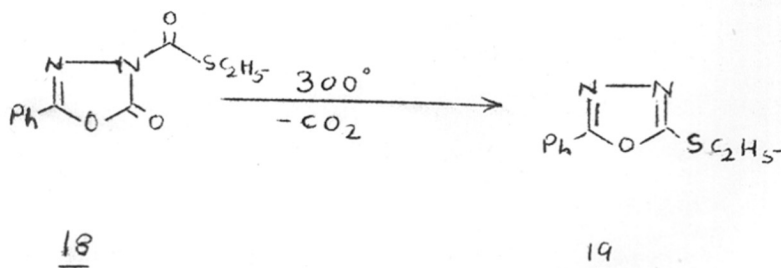
The reaction proceeds by thermal fragmentation of the oxadiazolone ring system to eliminate a molecule of CO₂ followed by cyclization of the 1,5 dipole 8 thus formed.

Recently Golfier et al. (10) reported the thermal conversion at $210-15^\circ$ in 2 hr. of 3-alkoxycarbonyl-5-phenyl-1,3,4-oxadiazol-2(3H)-ones 10 to 3-alkyl-5-phenyl-1,3,4-oxadiazol-2(3H)-ones 11 with a net loss of CO₂. They suggested the following mechanism for this transformation.



This mechanism, like that for the thermal decomposition of 7, involves the elimination of CO_2 by ring opening of 10 to produce the 1,3-dipole 12 which cyclizes to 14 through the isomeric 1,5-dipolar species 13. Compound 14, under the reaction conditions, is known for its 1,3-alkyl migration to form 11(11). The intermediate formation of 14 is confirmed by isolation of 15 and 16 (10,12) when the thermolysis is carried out in presence of methylene iodide and alkyl halides respectively. This mechanism, thus involves the thermal fragmentation of the oxadiazolone ring system at 215° itself, as against the higher temperatures of 280° being required for the decarboxylation of 7.

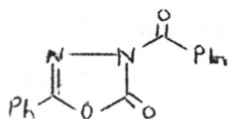
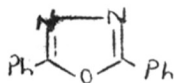
However, Golfier et al. observed that 3-phenoxy-carbonyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one 17 refused to decarboxylate even at 250° for 2 hr. while temperature, as high as 300° , was required for the thermal decarboxylation of 3-ethylthiocarbonyl-5-phenyl-1,3,4-oxadiazol-2 (3H)-one 18 to produce 2-ethylthio-5-phenyl-1,3,4-oxadiazole 19.



No explanation has been given by them for these significant observations.

PRESENT WORK

Due to the anomalous behaviour towards thermolysis of substituted triheteroatomic azoles as exemplified by the different temperatures required for the thermal decarboxylation of 7 and 10, it was thought of interest to scrutinize the thermostability of 3,5-disubstituted 1,3,4-oxadiazol-2(3H)-one ring system at 220°. The thermal stabilities of 7 and 10, with electronically similar substituents at position 3, would be expected to be alike. It has been observed that 3-benzoyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one 20, is quite stable at 220°, more than 80% being recovered

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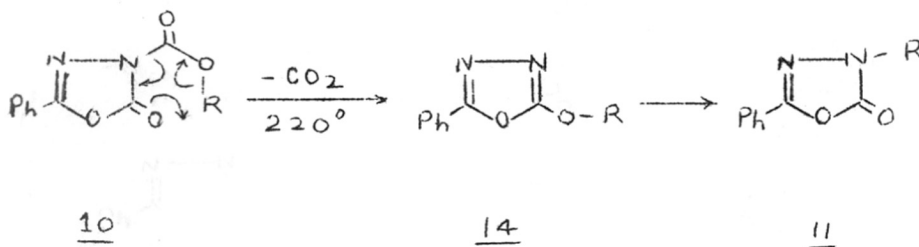
after 3 hr. by column chromatography. TLC indicated less than 10% conversion to 2,5-diphenyl-1,3,4-oxadiazole 21. Only above 250°, the rate of decomposition of 20 was significant and at 280-300°, 20 was smoothly converted to 21 in 4 hr.

Thus, this observation, along with the earlier reports of Sauer and Mayer (7), Remlinger (8) and Stolle (9) confirmed that the oxadiazolone ring system is fairly stable at 220° and temperatures above 250° are required for its thermal cleavage.

The mechanism suggested by Golfier et al.(10) for the thermal transformation of 10 to 11 with a net loss of CO_2 cannot explain the thermal stability of 17 even at 250° as well as the higher temperature of 300° which is required for the decarboxylation of 18. According to their mechanism, the thermal stability of the oxadiazolone ring in 17 and 18 would not be expected to be altered by a change in R_1 in 10 from alkyl to aryl or replacing OR_1 in 10 with SC_2H_5 ; this, however, is contradictory to their observations.

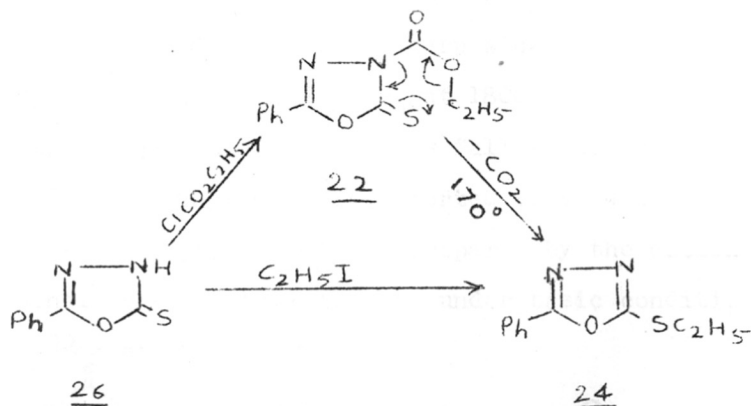
It thus became clear that the above reactions do not proceed according to the mechanism suggested by Golfier et al.(10) involving the cleavage of the ring system. It appeared more reasonable that the CO_2 that is lost, must be abstracted from the side chain alkoxycarbonyl group.

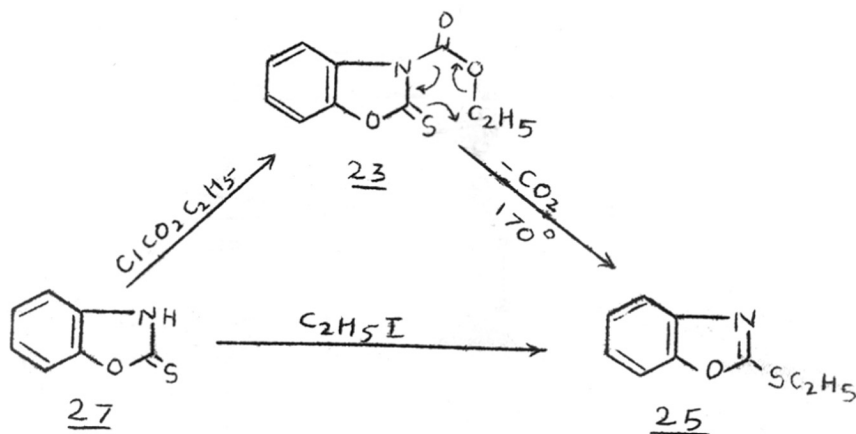
An alternative mechanism, as shown below, can be suggested to accommodate all the observations made by Golfier et al.(10). This mechanism involves thermal expulsion of CO_2 from the alkoxycarbonyl side-chain (and not by the cleavage of the oxadiazolone ring system) through a 6-membered transition state.



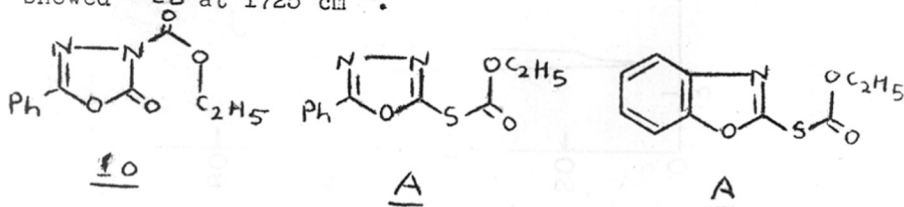
This mechanism also explains the thermal stability of 17 since the stable $\text{O}-\text{C}_6\text{H}_5$ bond would not be expected to cleave thermally under the conditions reported. Also at high temperatures (300°), the C_5-O bond in 18 breaks before the stronger $\text{S}-\text{C}_2\text{H}_5$ bond and thus 18 undergoes ring fragmentation by the mechanism suggested by Golfier et al. (10) to form 19.

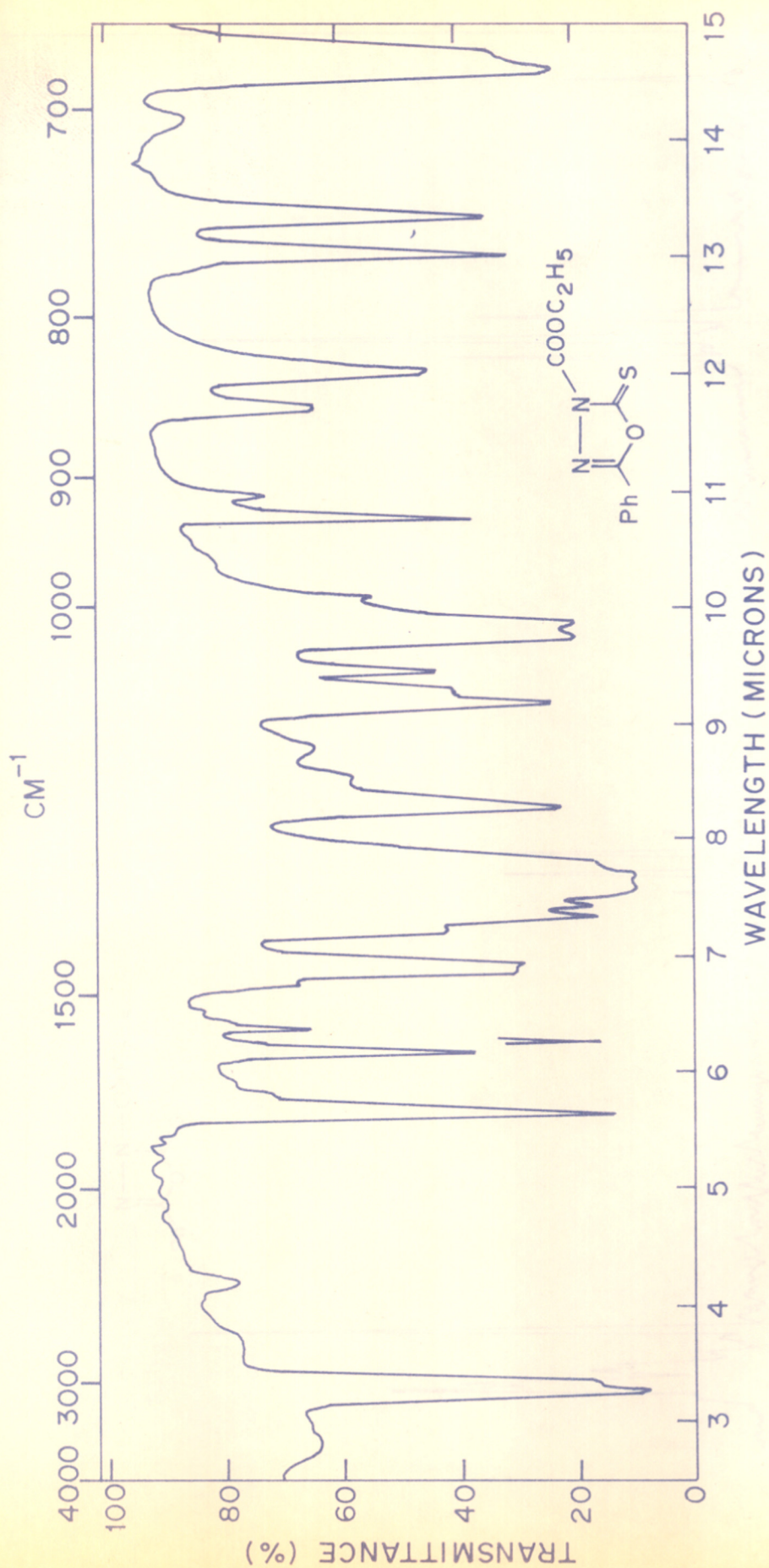
In order to gain further support for such a mechanism involving a 6-membered transition state, thermolysis of 3-ethoxycarbonyl-5-phenyl-1,3,4-oxadiazol-2(3H)-thione 22 and 3-ethoxycarbonyl-benzoxazol-2(3H)-thione 23 (13) was carried out at 170° for 3 hr. Both 22 and 23 under these conditions, underwent smooth elimination of CO_2 to give 2-ethylthio-5-phenyl-1,3,4-oxadiazole 24 (10) and 2-ethylthio-benzoxazole 25 (14) respectively. Compounds 24 and 25 were characterized by their identity with authentic samples prepared by ethylation of 5-phenyl-1,3,4-oxadiazol-2(3H)-thione 26 (15) and benzoxazol-2(3H)-thione 27 (16) respectively.

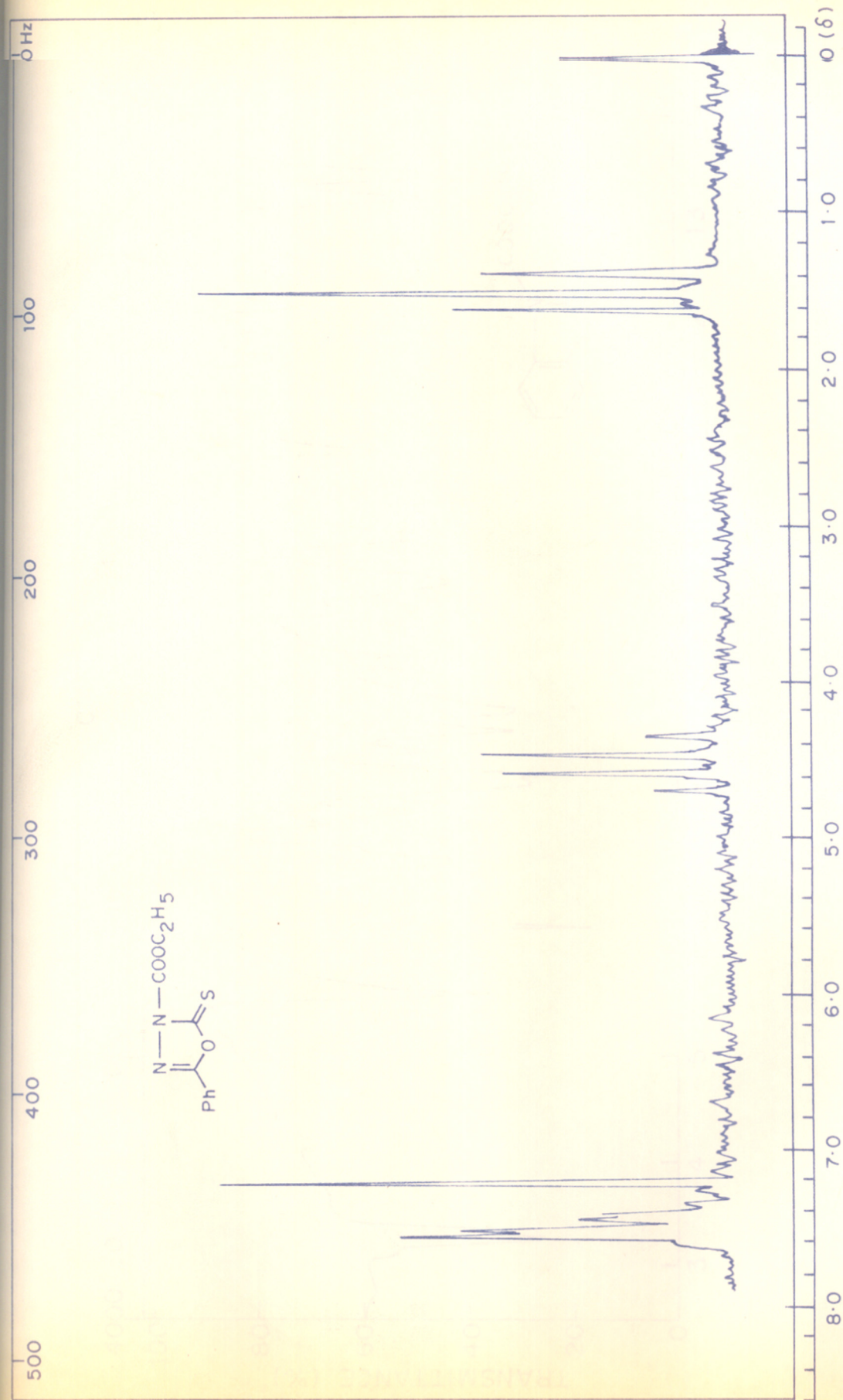


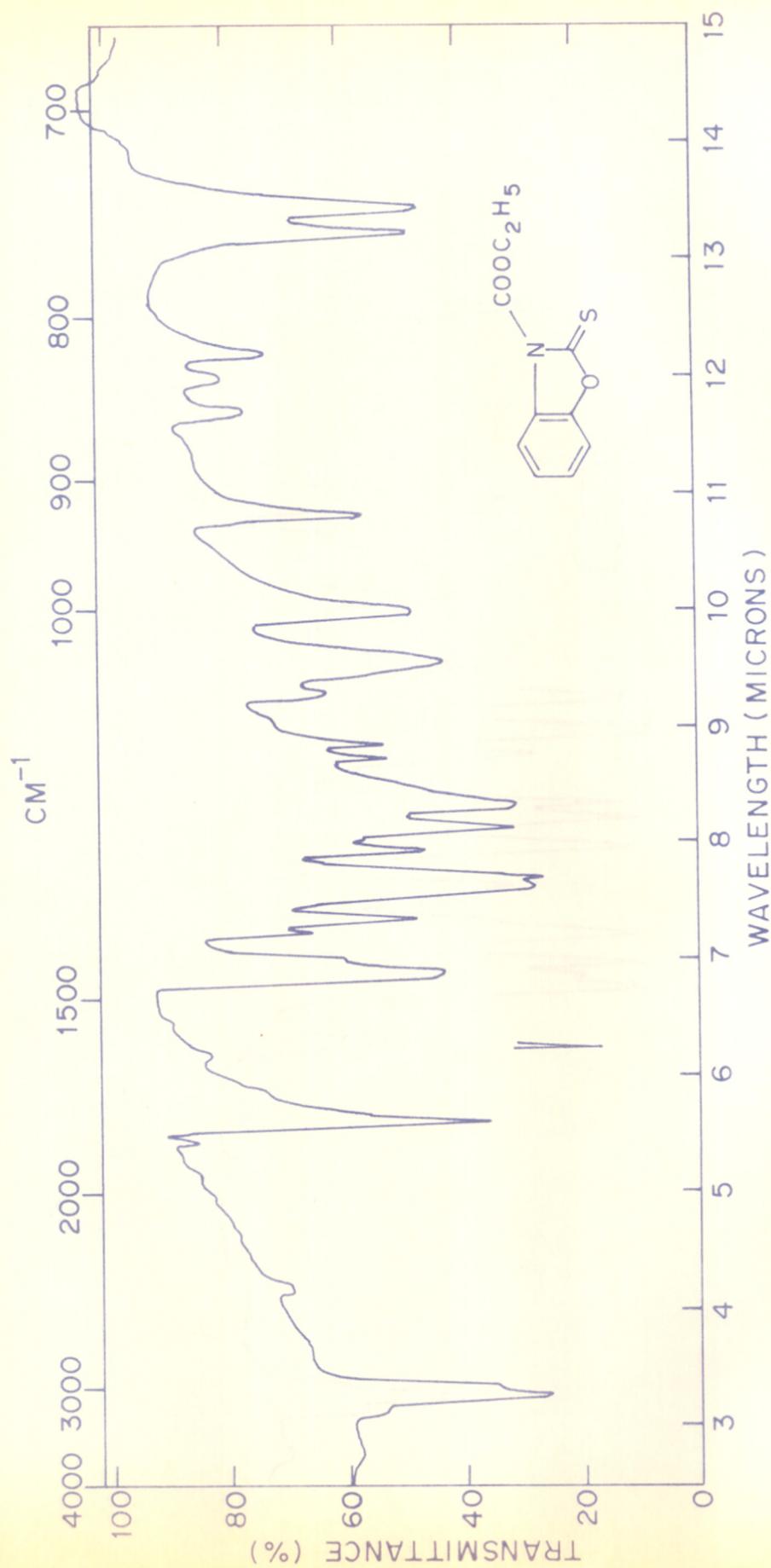


That, compounds 22 and 23, prepared by the treatment of 26 and 27 respectively with ethyl chloroformate either by refluxing neat or in benzene containing triethylamine, have the structures shown and not the alternative thicarbonate structures such as A became clear from the study of their IR spectra in comparison with those of related substances. The high values of $\nu_{\text{C=O}}$ at 1760 cm^{-1} in 22 and 1770 cm^{-1} in 23 as sharp peaks were similar to the side chain $\nu_{\text{C=O}}$ of 10 ($\text{R} = \text{C}_2\text{H}_5$) (10) which shows a sharp singlet at 1760 cm^{-1} apart from the ring doublet $\nu_{\text{C=O}}$ at 1800 and 1820 cm^{-1} . In contrast, $\nu_{\text{C=O}}$ of thicarbonates fall in the range $1718\text{--}1734\text{ cm}^{-1}$. (17). $\text{CH}_3\text{SCOOCH}_3$ is reported to show a singlet at 1718.8 cm^{-1} (17). $\text{C}_6\text{H}_5\text{SCOOC}_2\text{H}_5$, prepared by the action of thiophenol on ethylchloroformate under basic conditions, showed $\nu_{\text{C=O}}$ at 1725 cm^{-1} .

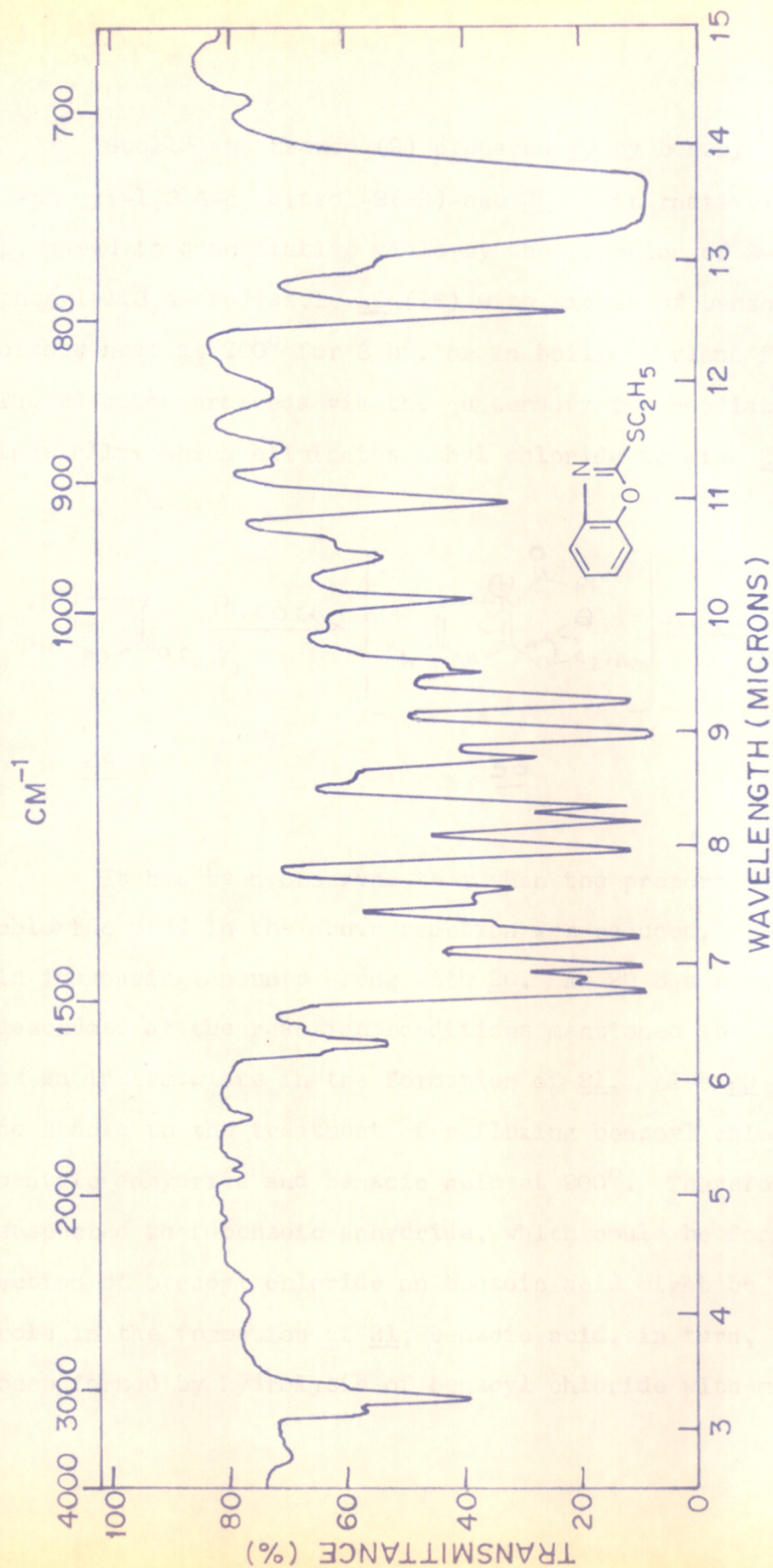


IR OF COMPOUND 22

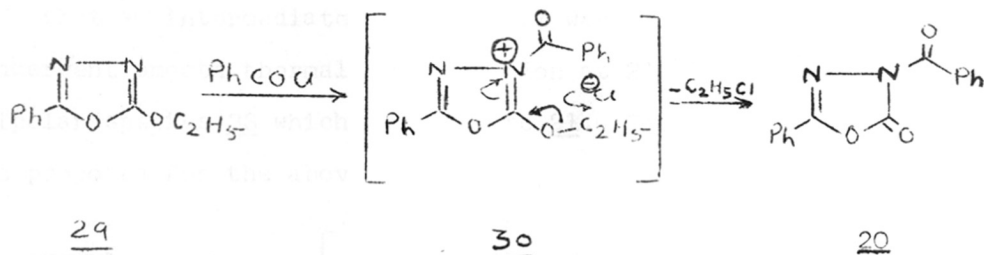




IR OF COMPOUND 23

IR OF COMPOUND 25

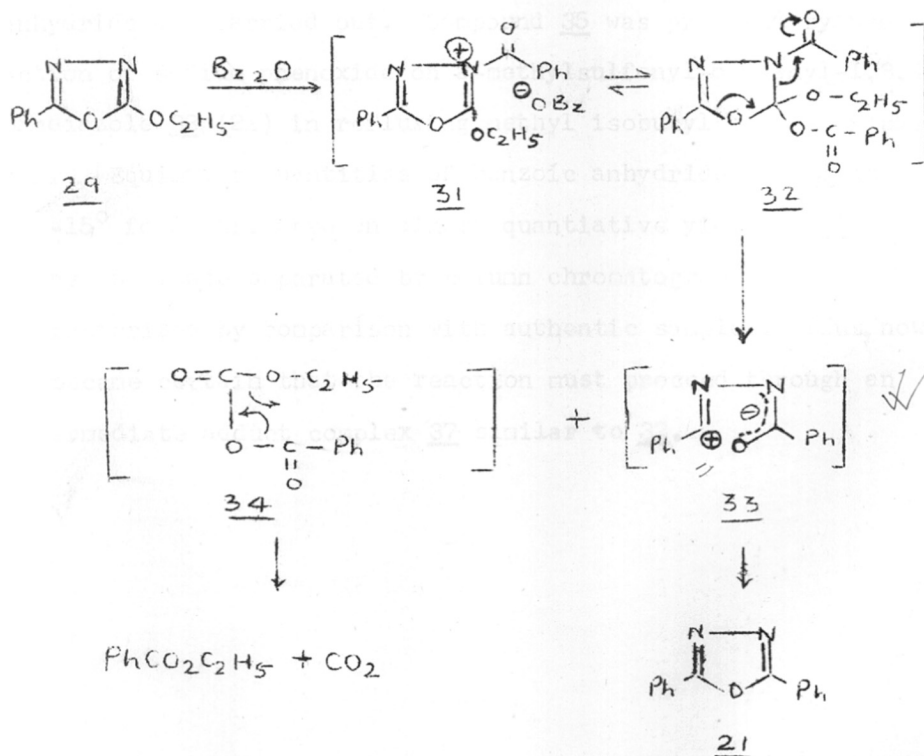
Stolle and Krauch (9) prepared 20 by benzoylation of 5-phenyl-1,3,4-oxadiazol-2(3H)-one 28. Alternatively, 20 was prepared in quantitative yield by the reaction of 2-ethoxy-5-phenyl-1,3,4-oxadiazole 29 (18) with excess of benzoyl chloride, either neat at 200° for 3 hr. or in boiling xylene for 24 hr. The reaction proceeds via the quaternary intermediate 30 formed initially, which eliminates ethyl chloride to give 20.



It has been observed that when the proportion of benzoyl chloride used in the above reaction was reduced, 21 was formed in increasing amounts along with 20. As 20 has been proved not to decompose at the reaction conditions mentioned above, it could not be an intermediate in the formation of 21. Also 20 was found to be stable to the treatment of refluxing benzoyl chloride, benzoic anhydride and benzoic acid at 200°. Therefore, it was suspected that benzoic anhydride, which could be formed by the action of benzoyl chloride on benzoic acid might be playing some role in the formation of 21; benzoic acid, in turn, could have been formed by hydrolysis of benzoyl chloride with moisture.

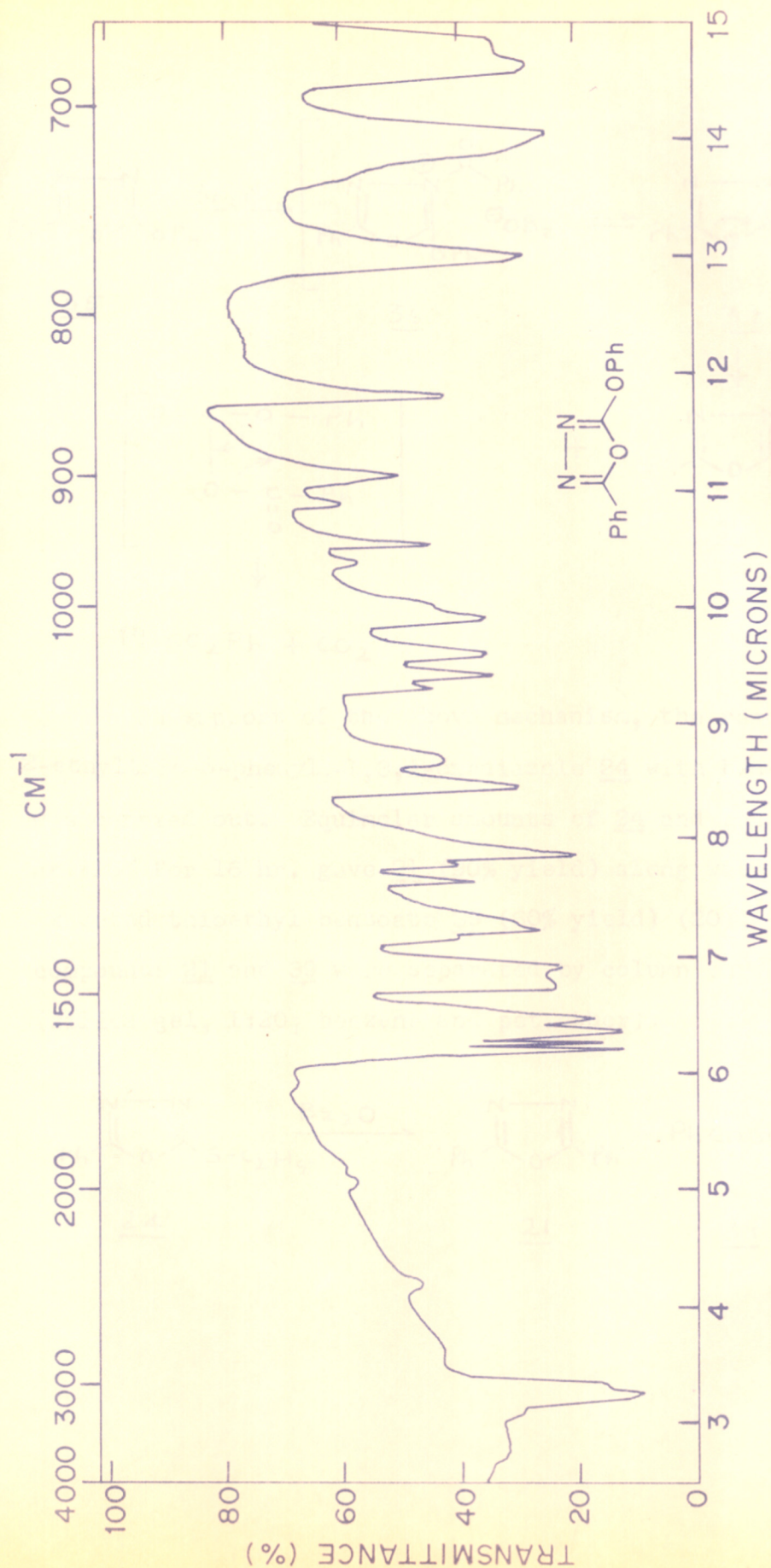
So the reaction of benzoic anhydride with 29 was carried out. In this reaction at $210-15^{\circ}$ for 3 hr., the major product was 21 (67% yield) along with 20 (33% yield). The products were separated by column chromatography (silica gel, 1:15 chloroform/pet.ether, 3:7 and 4:1) and characterized by mixed m.p., superimposable IR, NMR and M^{+} ion with authentic samples.

It thus became clear that OBz^{-} ion was playing a role different from that of Cl^{-} ion in the benzoyl chloride reaction and that an intermediate or a complex was being formed which underwent smooth thermal fragmentation at $210-15^{\circ}$ to the 1,5-dipolar species 33 which cyclized to 21. The following mechanism is proposed for the above reaction.

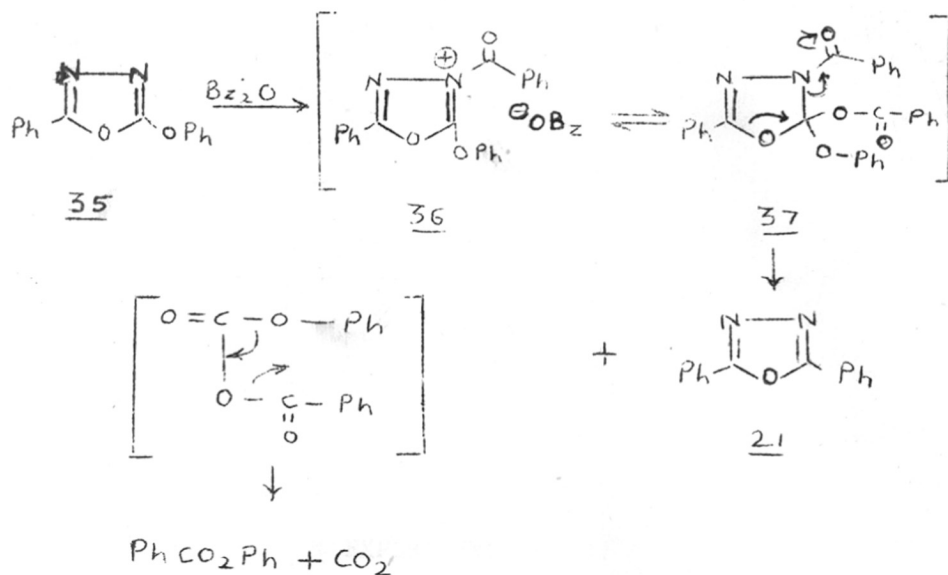


The nitrogen atom at 3 position in 29, being sufficiently nucleophilic, attacks a molecule of benzoic anhydride to form a quaternary complex 31 which by the attack of OBz^- ion at C_2 forms 32 in equilibrium concentrations. Adduct 32 then undergoes smooth thermolysis at $210-15^\circ$ and forms the 1,5-dipolar species 33 along with the compound 34. The dipole 33 then cyclizes to 21 while 34 decomposes to produce CO_2 and ethyl benzoate. Smaller quantities of 20 are formed from the quaternary complex 31 just as in the case of 30.

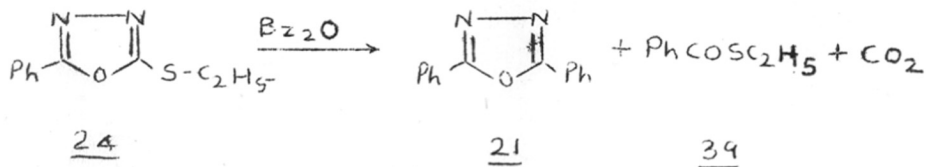
In order to suppress the formation of 20 which cannot be formed from 2-phenoxy-5-phenyl-1,3,4-oxadiazole 35 (19) through the quaternary complex 36, the reaction of 35 with benzoic anhydride was carried out. Compound 35 was prepared by the action of sodium phenoxide on 2-methylsulfonyl-5-phenyl-1,3,4-oxadiazole 38 (21) in refluxing methyl isobutyl ketone (MIBK) for 5 hr. Equimolar quantities of benzoic anhydride and 35 at $210-15^\circ$ for 8 hr. gave an almost quantitative yield of 21 and phenyl benzoate separated by column chromatography and characterized by comparison with authentic samples. Thus, now it became certain that the reaction must proceed through an intermediate adduct complex 37 similar to 32.



IR OF COMPOUND 35



In support of the above mechanism, the reaction of 2-ethylthio-5-phenyl-1,3,4-oxadiazole 24 with benzoic anhydride was carried out. Equimolar amounts of 24 and benzoic anhydride at 215° for 16 hr. gave 21 (90% yield) along with the expected thioethyl benzoate 39 (60% yield) (20). The compounds 21 and 39 were separated by column chromatography (silica gel, 1:20; benzene and pet. ether).



Preparation of 3-benzoyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one 20

(a) 2-Ethoxy-5-phenyl-1,3,4-oxadiazole 29 (19) (0.95 g; 0.005 M) was refluxed in excess of benzoyl chloride (10 ml) for 10 hr. The unreacted benzoyl chloride was then distilled under reduced pressure (40 mm); the last traces were removed under high vacuum. A solid was obtained which was crystallized from alcohol.

Yield: 1.290 (97%) m.p. 130° [Lit. 130(9)]

(b) A mixture of compound 29 (0.95 g, 0.005 M) and benzoyl chloride (0.7 g; 0.005 M) was refluxed in 15 ml. xylene for 24 hr. Xylene was then distilled at 40 mm when the residue solidified. It was crystallized from alcohol.

Yield: 1.3 g (98%) m.p. 130°

The solids obtained by methods (a) and (b) showed no depression in their mixed m.p.

These solids showed superimposable IR, ^1H NMR and Mass spectra and undepressed mixed m.p. with the authentic sample prepared by benzoylation of 5-phenyl-1,3,4-oxadiazol-2(3H)-one (9). Thermolysis of 20.

(a) at 220°

Compound 20 (0.532 g; 0.002 M) was heated in an oil bath at 220° for 3 hr. under nitrogen atmosphere. The reaction mixture was then chromatographed over silica gel (1:15) with chloroform + pet.ether (3:7 and 4:1) as eluents. Evaporation of the earlier fraction gave the starting compound 20 (0.45 g; 85%) while 2,5-diphenyl-1,3,4-oxadiazole 21 (30 mg; 7%) was obtained from the latter fraction.

Compound 21: m.p. 140 $^{\circ}$ [Lit. 140 $^{\circ}$ (20)]

Compound 21 showed superimposable IR, ^1H NMR and Mass spectra and undepressed mixed m.p. with the authentic sample prepared by cyclodehydration of sym.-dibenzoylhydrazine (20).

(b) At 300 $^{\circ}$

A similar thermolysis of 20 (0.532 g; 0.002 M) was carried out at 300 $^{\circ}$ for 4 hr. The dark residue, on passing through silica gel column (1:15), gave the compound 21 (0.48 g; 90%) from chloroform + pet.ether (4:1) fraction.

(c) With benzoyl chloride

Compound 20 (0.532 g; 0.002 M) was refluxed in excess of benzoyl chloride (10 ml) for 3 hr. After the reaction, benzoyl chloride was distilled under reduced pressure. The residual solid was dissolved in chloroform, washed repeatedly with 10% sodium bicarbonate solution and then with water, dried (Na_2SO_4) and chloroform evaporated when pure starting compound 20 was recovered.

Yield: 0.510 g (96%).

(d) With benzoic anhydride

A mixture of compound 20 (0.532 g; 0.002 M) and benzoic anhydride (0.904 g; 0.004 M) was heated in an oil bath at 200 $^{\circ}$ for 3 hr. Then a similar work out as in (c) gave 0.490 g (92%) of 20.

(e) With benzoic acid

A mixture of compound 20 (0.532 g; 0.002 M) and benzoic acid (0.488 g; 0.004 M) was heated in an oil bath at 200 $^{\circ}$ for 3 hr. Following a similar workout as in (c) gave 0.5 g (94%) of 20.

Preparation of 3-ethoxycarbonyl-5-phenyl-1,3,4-oxadiazol-2

(3H)-thione 22

(a) 5-Phenyl-1,3,4-oxadiazol-2 (3H)-thione 26 (16) (0.534 g; 0.003 M) was refluxed in excess of ethyl chloroformate (10 ml) for 12 hr. The unreacted ethyl chloroformate was then distilled under reduced pressure when a solid mass was obtained. It was crystallized from benzene + pet.ether (1:1) when colourless needles of 22 were obtained.

Yield: 0.525 g (70%); m.p. 147°.

(b) A mixture of 26 (0.534 g; 0.003 M), ethyl chloroformate (0.324 g; 0.003 M) and triethylamine (0.303 g; 0.003 M) was refluxed in benzene (20 ml) for 3 hr. The solid triethylamine hydrochloride was then filtered out. The filtrate was washed with water, dried (Na_2SO_4) and benzene evaporated when a solid was obtained. It was crystallized from benzene + pet.ether (1:1) into fine needles of 22.

Yield: 0.675 g (90%); m.p. 147°.

The needles obtained by methods (a) and (b) showed no depression in their mixed m.p.

Elemental analyses: Found C = 52.54%; H = 4.08%; N = 11.11%

$\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_3\text{S}$ requires C = 52.80%; H = 4.00%;
N = 11.20%.

U.V.: λ_{max} 286 nm (log ϵ 4.2).

I.R. ($\nu_{\text{max}}^{\text{nujol}}$): 1770 (carbonyl); 1620 (C = N).

^1H NMR (CDCl_3): 7.76 - 8.0 (m, 2H) and 7.26 - 7.56 (m, 3H) (aromatic protons); 4.46 (q, J = 8 Hz, 2H, methylene protons); 1.46 (t, J = 8 Hz, 3H, methyl protons).

M^+ ion: 250.

Preparation of 3-ethoxycarbonyl-benzoxazol-2(3H)-thione 23

Compound 23 was prepared from benzoxazol-2 (3H)-thione 27 (17) in 70% yield by both the methods (a) and (b) similar to 22.

Compound 23: m.p. 96° [Lit. $93-4^{\circ}$ (13)]

Thermolysis of 22

Compound 22 (0.5 g; 0.002 M) was heated in an oil bath at 170° for 3 hr. The reaction was accompanied by evolution of a gas (CO_2). After the reaction, the oil was chromatographed over silica gel (1:20). Elution with benzene + chloroform (4:1) gave 2-ethylthio-5-phenyl-1,3,4-oxadiazole 24 (0.270 g; 65%) m.p.: $39-40^{\circ}$.

Compound 24 thus obtained, showed superimposable IR, ^1H NMR and Mass spectra and undepressed mixed m.p. with the authentic sample prepared by ethylation of 26 (10).

Thermolysis of 23

Compound 23 (0.446 g; 0.002 M) was heated in an oil bath at 170° . The reaction was accompanied by evolution of a gas (CO_2). After the gas evolution ceased (3 hr) the resulting reaction mixture was chromatographed over silica gel column (1:15). Elution with pet. ether + chloroform (7:3) gave 2-ethylthiobenzoxazole 25 (0.32 g; 90%) m.p. 49° .

Compound 25 showed superimposable IR, ^1H NMR and mass spectra and undepressed mixed m.p. with the authentic sample prepared by ethylation of 27 (15).

Reaction of 2-ethoxy-5-phenyl-1,3,4-oxadiazole 29 with (1:1) benzoyl chloride

A mixture of compound 29 (19) (0.38 g; 0.002 M) and benzoyl chloride (0.28 g; 0.002 M) was heated in an oil bath at 200° for 5 hr. The reaction mixture was then chromatographed over silica gel column (1:15). Elution with chloroform + pet. ether (3:7) gave compound 20 (0.37 g; 70%) while 21 (0.065 g; 15%) was obtained by evaporation of chloroform + pet. ether (4:1) fraction.

Reaction of benzoic anhydride with 29

A mixture of benzoic anhydride (0.452 g; 0.002 M) and compound 29 (0.38 g; 0.002 M) was heated in an oil bath at 210-15° for 3 hr. The oily mass was then chromatographed over silica gel (1:15) column. Elution with pet. ether gave ethyl benzoate (0.22 g; 74%). Elution with chloroform + pet. ether (3:7) gave the compound 20 (0.175 g; 33%) while 21 (0.3 g; 67%) was obtained from the chloroform + pet. ether (4:1) fraction.

Preparation of 2-phenoxy-5-phenyl-1,3,4-oxadiazole 35

Phenol (0.207 g; 0.0022 M) was dissolved in MIBK and sodium hydroxide (0.080 g; 0.002 M) dissolved in minimum quantity of water was added to it. Water was then removed azeotropically and to the resulting MIBK solution 2-methylsulfonyl-5-phenyl-1,3,4-oxadiazole 38 (21) (0.448 g; 0.002M) was added. The reaction mixture was then refluxed for 5 hr. MIBK was then distilled under vacuum. The residue was then extracted with ether (3 x 150 ml). The ether extract was then

washed with water, 10% sodium hydroxide. solution, again with water and dried (Na_2SO_4). Evaporation of ether gave a coloured residue which was crystallized from pet.ether.

Yield: Compound 35 (0.285 g; 60%).

m.p. 76° /Lit. 76° (19)7

Reaction of benzoic anhydride with 35

A mixture of benzoic anhydride (0.452 g; 0.002 M) and 35 (0.476 g; 0.002 M) was heated in an oil bath at 215° for 8 hr. The reaction was TLC monitored; the starting compound 35 disappeared after 8 hr. The reaction mixture was then passed through silica gel (1:10) column. Elution with pet.ether gave phenyl benzoate (0.355 g; 90%) while 21 (0.420 g; 95%) was obtained from benzene + chloroform (1:1) fraction.

Phenyl benzoate, thus obtained, was identical with the authentic sample 20 (IR, VPC and mixed m.p.).

Reaction of benzoic anhydride with 24

A mixture of benzoic anhydride (0.452 g; 0.002^f M) and 24 (0.412 g, 0.002 M) was heated in an oil bath at 220° for 16 hr. under nitrogen atmosphere. Then the coloured mass was chromatographed over silica gel (1:20) column using pet.ether and chloroform as eluents. The pet.ether fraction gave thioethyl benzoate 39 (21) (0.2 g; 60%) while 21 (0.4 g; 90%) was obtained by evaporation of chloroform fraction.

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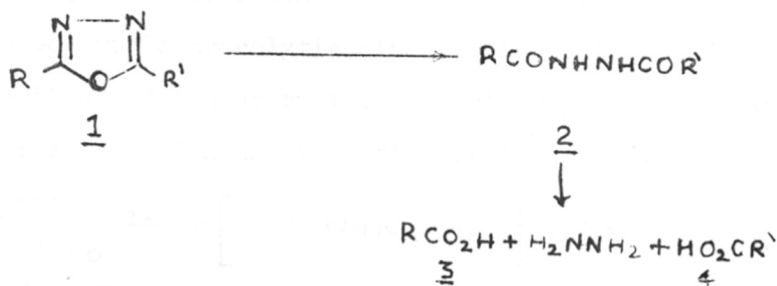
CHAPTER V

REACTIONS OF NUCLEOPHILES WITH 1,3,4-
OXADIAZOLE DERIVATIVES

INTRODUCTION

The 1,3,4-oxadiazole ring system is extremely labile to a variety of chemical agents. The ring cleavage reactions of 1,3,4-oxadiazole derivatives can be achieved by the action of reducing agents or by nucleophiles. Generally, N-N bond fission takes place with reducing agents, thus resulting with amide formation while with nucleophiles, C-O bond gets cleaved. The ring opening tendency is controlled by the electron density at the C₂ or C₅ atom, which is largely dependent on the substituents.

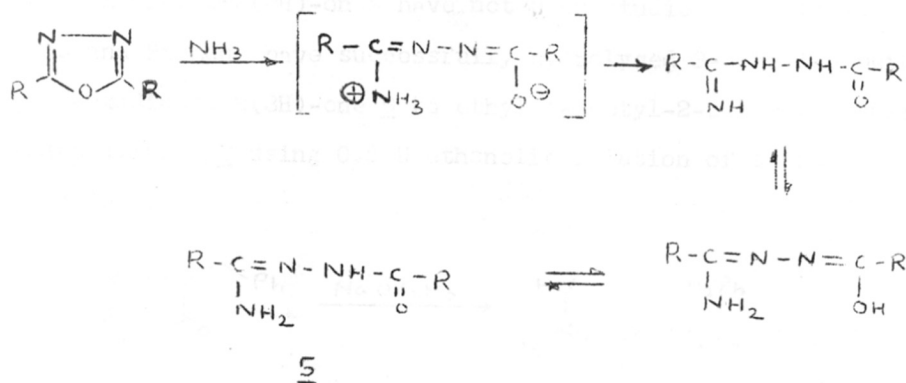
Ring cleavage of 2,5-dialkyl-1,3,4-oxadiazoles 1 can be achieved with either an acid or a base leading to acid hydrazides 2 or the respective carboxylic acids 3, 4 and hydrazine (1).



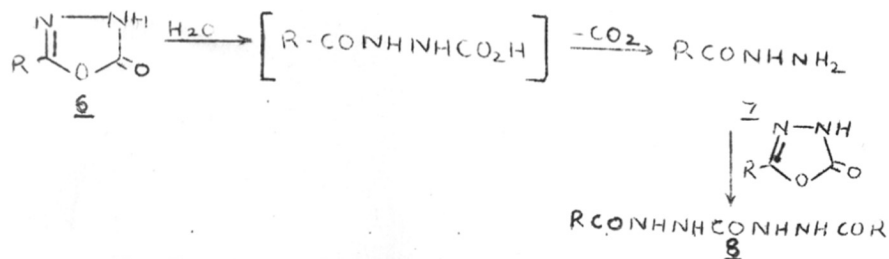
In general it is found that the aryl substituted 1,3,4-oxadiazoles are less sensitive to acids (2).

Nucleophiles like ammonia or methylamine also easily cleave the 1,3,4-oxadiazole ring system (3). Nucleophilic attack by ammonia apparently occurs at the ring carbon atom

and produces the ring opened product 5.

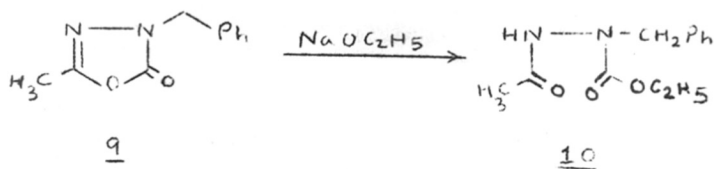


Similar to the 2,5-disubstituted-1,3,4-oxadiazoles, the ring cleavage of 5-substituted-1,3,4-oxadiazol-2(3H)-ones 6 can be achieved by the action of nucleophiles such as ammonia, amines (4) and hydrazine (5). The reaction path apparently proceeds via a hydrolytic ring opening with hydrazide 7 formation and the hydrazide then cleaves the remaining unchanged oxadiazolone with the formation of 1,5-diacylcarbohydrazide 8.



The 5-substituted-1,3,4-oxadiazol-2(3H)-thiones are less reactive than the corresponding 5-substituted-1,3,4-oxadiazol-2(3H)-ones. Ring opening to the thiosemicarbazide derivatives is possible using p-toluidine, hydrazines or thiocarbohydrazide (6).

The action of nucleophiles on some 3,5-disubstituted-1,3,4-oxadiazol-2(3H)-ones have not been studied in detail. Kurtz and Niemann have successfully hydrolysed 3-benzyl-5-methyl-1,3,4-oxadiazol-2(3H)-one 9 to ethyl 1-acetyl-2-benzyl-hydrazin-2-carboxylate 10 using 0.5 N ethanolic solution of sodium ethoxide (7).

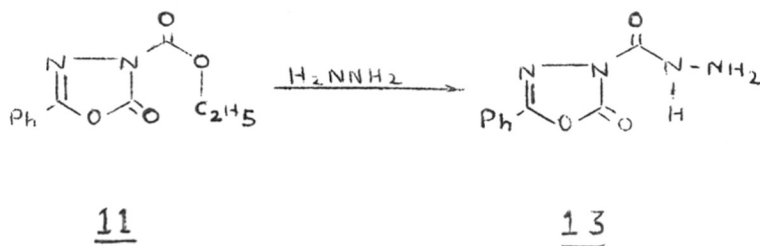


PRESENT WORK

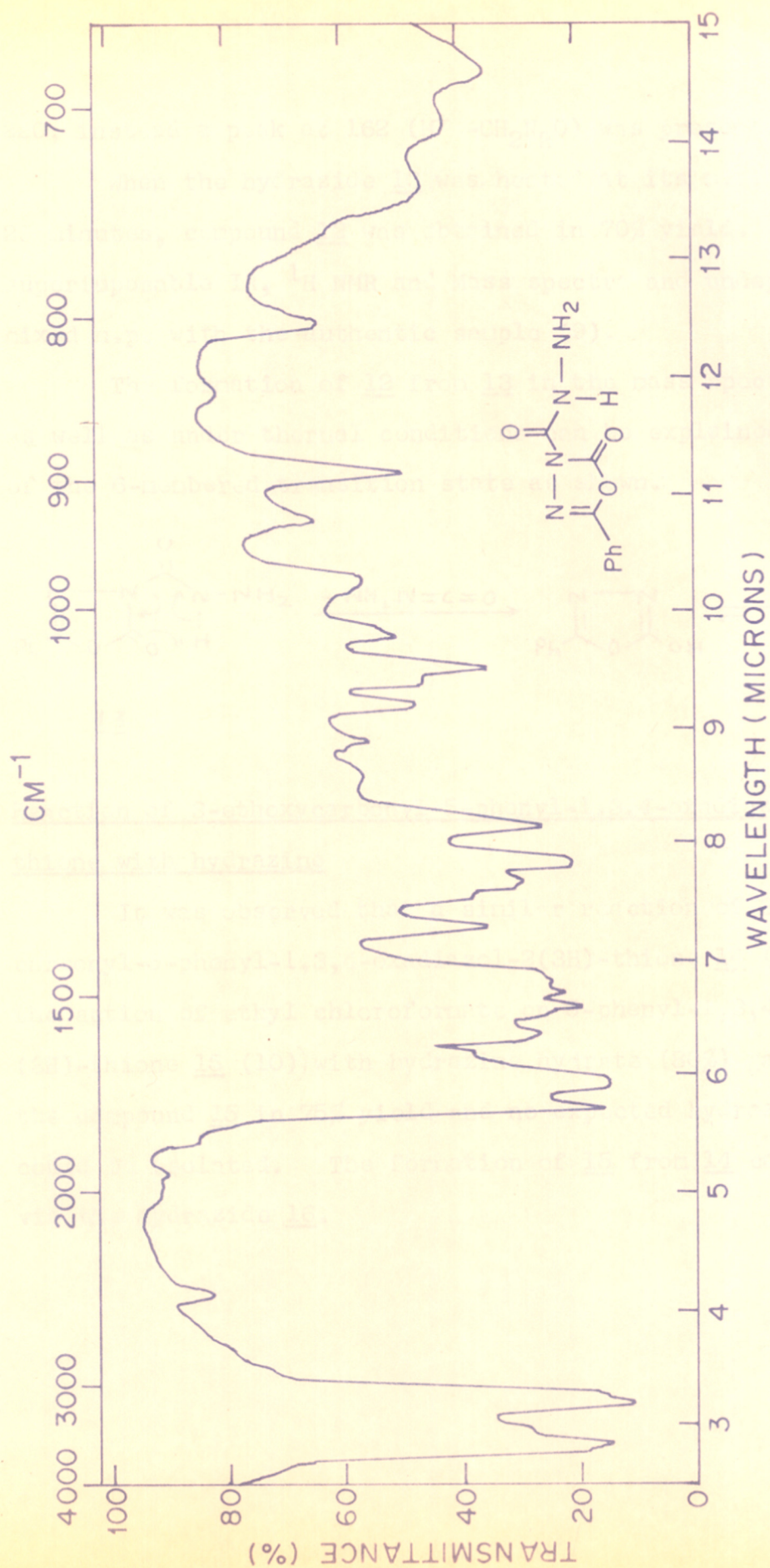
Due to a very few reports in literature of nucleophilic ring opening reactions of 3,5-disubstituted-1,3,4-oxadiazol-2(3H)-ones and 3,5-disubstituted-1,3,4-oxadiazol-2(3H)-thiones, it was worthwhile to see the behaviour of such compounds towards the nucleophilic agents like hydrazine and triethylamine.

Reaction of 3-ethoxycarbonyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one with hydrazine

3-Ethoxycarbonyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one 11 (8), prepared by the action of ethyl chloroformate on 5-phenyl-1,3,4-oxadiazol-2(3H)-one 12, on refluxing in ethanol containing equimolar amount of hydrazine hydrate (80%) gave the corresponding hydrazide 13.



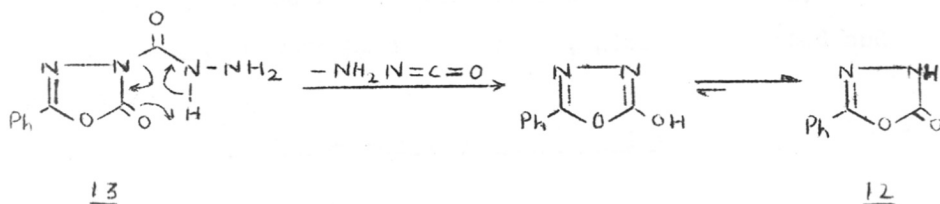
The hydrazide 13 melted at 155° with decomposition. It gave satisfactory elemental analyses. Its IR spectrum showed a peak at 3500 cm⁻¹ for NH stretching along with the carbonyl frequencies at 1755 cm⁻¹ and 1660-1690 (broad) cm⁻¹ for the ring carbonyl and the side chain carbonyl groups respectively. Its ¹H NMR in TFA showed signals at δ 7.26 - 7.83 for 5 aromatic protons. However, its mass spectrum did not show the M⁺ ion at

IR OF COMPOUND 13

220; instead a peak at 162 ($M^+ - CH_2N_2O$) was present.

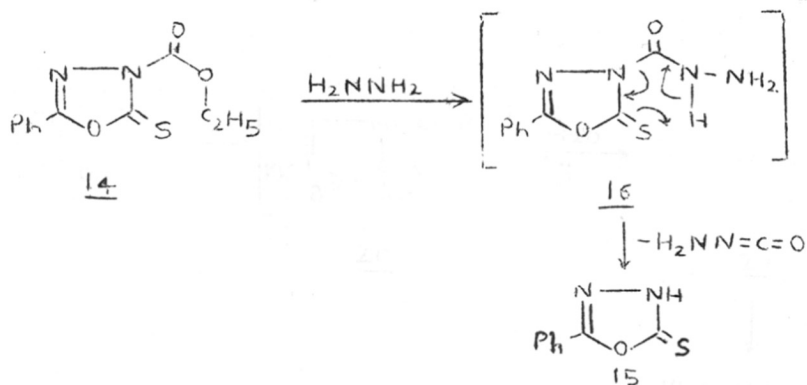
When the hydrazide 13 was heated at its m.p. for 20 minutes, compound 12 was obtained in 70% yield. It gave superimposable IR, 1H NMR and Mass spectra and undepressed mixed m.p. with the authentic sample (9).

The formation of 12 from 13 in the mass spectrometer as well as under thermal conditions can be explained on the basis of the 6-membered transition state as shown.



Reaction of 3-ethoxycarbonyl-5-phenyl-1,3,4-oxadiazol-2(3H)-thione with hydrazine

It was observed that a similar reaction of 3-ethoxycarbonyl-5-phenyl-1,3,4-oxadiazol-2(3H)-thione 14 (prepared by the action of ethyl chloroformate on 5-phenyl-1,3,4-oxadiazol-2(3H)-thione 15 (10)) with hydrazine hydrate (80%) gave directly the compound 15 in 75% yield and no expected hydrazide 16 could be isolated. The formation of 15 from 14 can be explained via the hydrazide 16.

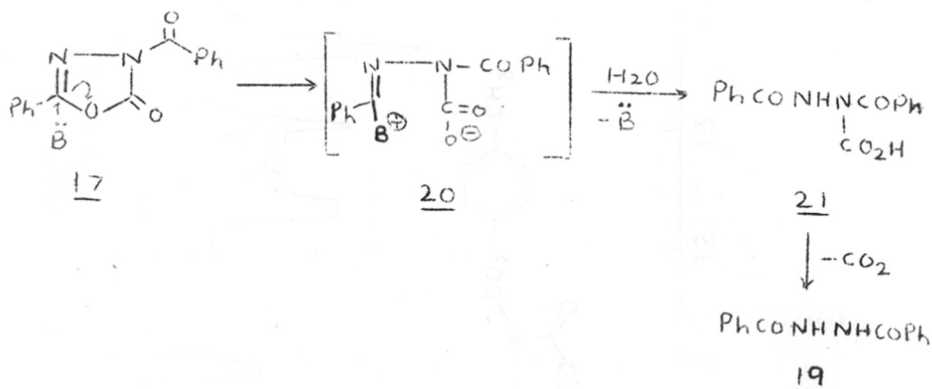


Possibly, due to the strong tendency of S to abstract hydrogen atom through the 6-membered transition state, the hydrazide **16**, as soon as it is formed, gets degenerated and produces **15**.

Reaction of 3-benzoyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one with nucleophiles

3-Benzoyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one **17** was prepared by the action of benzoyl chloride on 2-ethoxy-5-phenyl-1,3,4-oxadiazole **18** either neat at 200° for 3 hr. or in refluxing xylene for 24 hr. The compound **17**, on refluxing in ethanol containing equimolar amount of hydrazine hydrate (80%) or triethylamine, produced the ring opened 1,2-dibenzoyl hydrazine **19**. This showed superimposable IR spectrum and undepressed mixed m.p. with the authentic sample prepared by benzoylation of benzhydrazide (11).

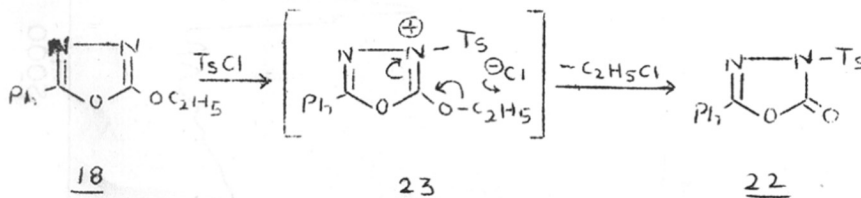
The formation of **19** from **17** may be explained on the basis of the following mechanism.



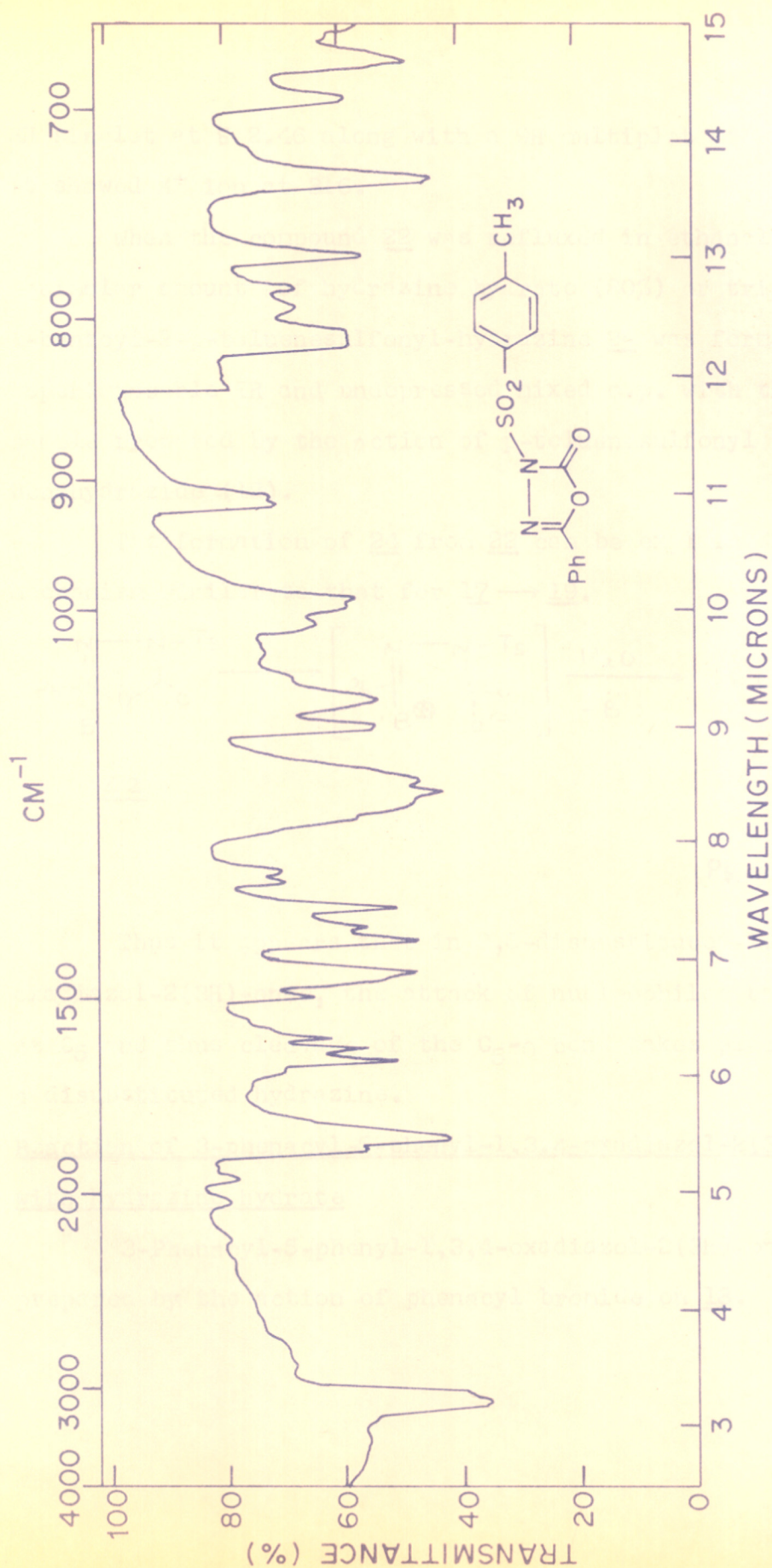
The nucleophile B attacks at C₅ and the ring opening takes place with the cleavage of C₅-O bond resulting in the formation of the species 20 which then gets hydrolysed to 21. Compound 21 gets easily decarboxylated and forms 19.

Reaction of 5-phenyl-3-p-toluenesulfonyl-1,3,4-oxadiazol-2(3H)-one with nucleophiles

The compound 18 when treated with p-toluenesulfonyl chloride in refluxing xylene gave 5-phenyl-3-p-toluenesulfonyl-1,3,4-oxadiazol-2(3H)-one 22 in 90% yield. The reaction goes via the quaternary complex 23 which eliminates a molecule of ethyl chloride.



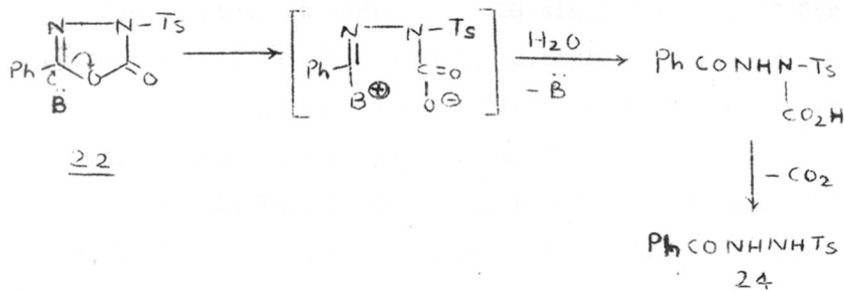
The compound 22 in its IR spectrum showed carbonyl frequency at 1810 cm⁻¹. In its ¹H NMR spectrum it showed a

IR OF COMPOUND 22

3H singlet at δ 2.46 along with a 9H multiplet at δ 7.23 - 8.20. It showed M^+ ion at 316.

When the compound 22 was refluxed in ethanol containing equimolar amount of hydrazine hydrate (80%) or triethylamine, 1-benzoyl-2-p-toluenesulfonyl-hydrazine 24 was formed. It gave superimposable IR and undepressed mixed m.p. with the authentic sample prepared by the action of p-toluenesulfonyl chloride on benzhydrazide (12).

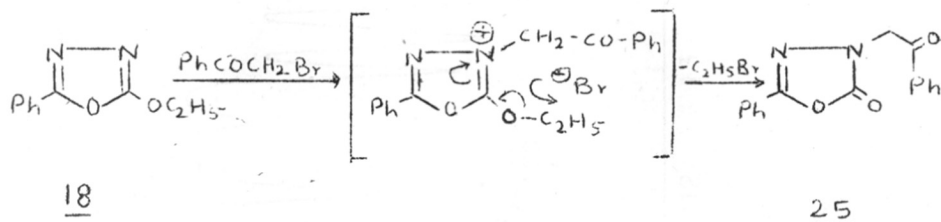
The formation of 24 from 22 can be explained by a mechanism similar to that for 17 $\rightarrow$ 19.



Thus it appears that in 3,5-disubstituted-1,3,4-oxadiazol-2(3H)-ones, the attack of nucleophiles takes place at C_5 and thus cleavage of the C_5-O bond takes place to produce a disubstituted hydrazine.

Reaction of 3-phenacyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one with hydrazine hydrate

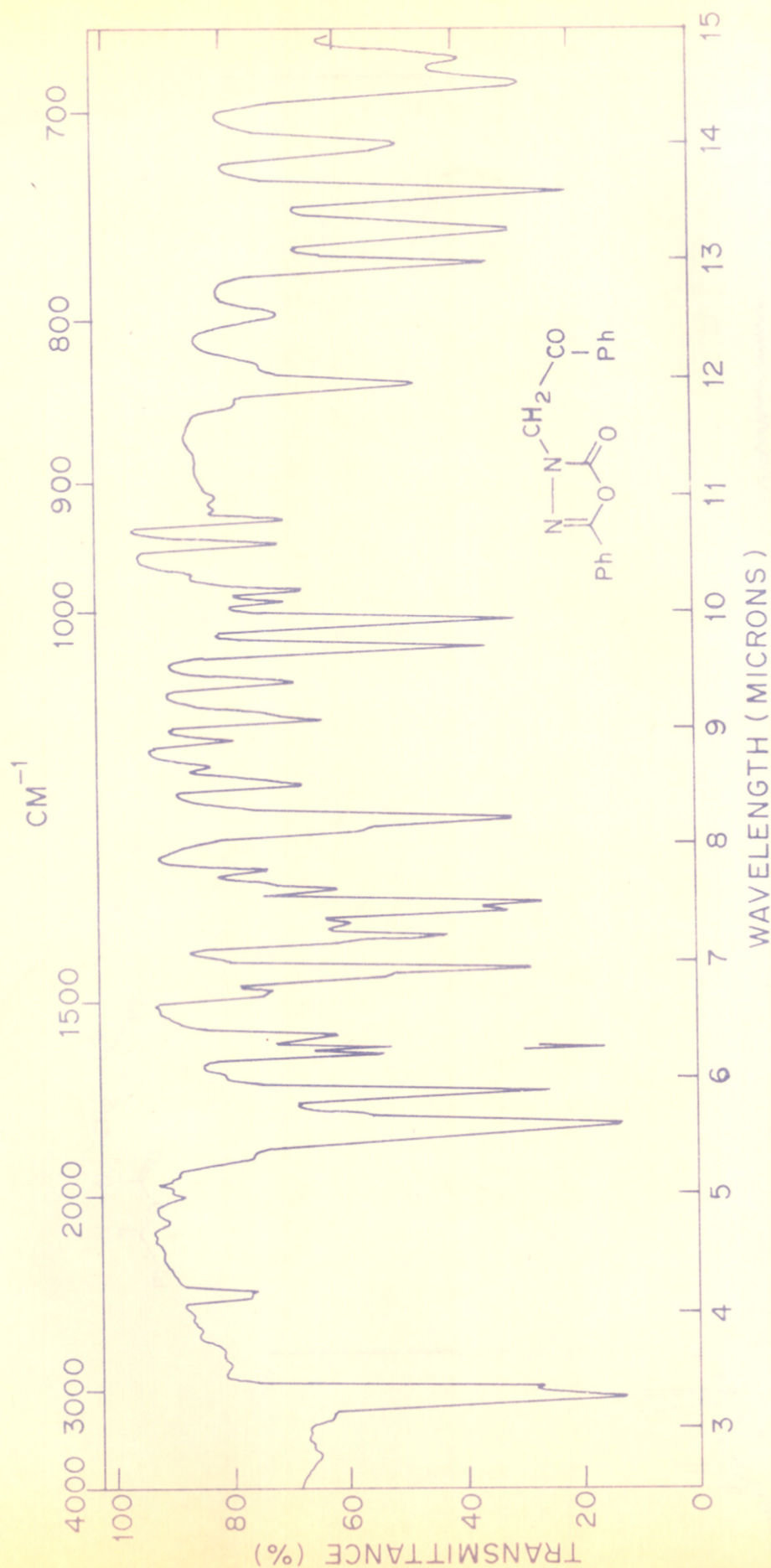
3-Phenacyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one 25 was prepared by the action of phenacyl bromide on 18.



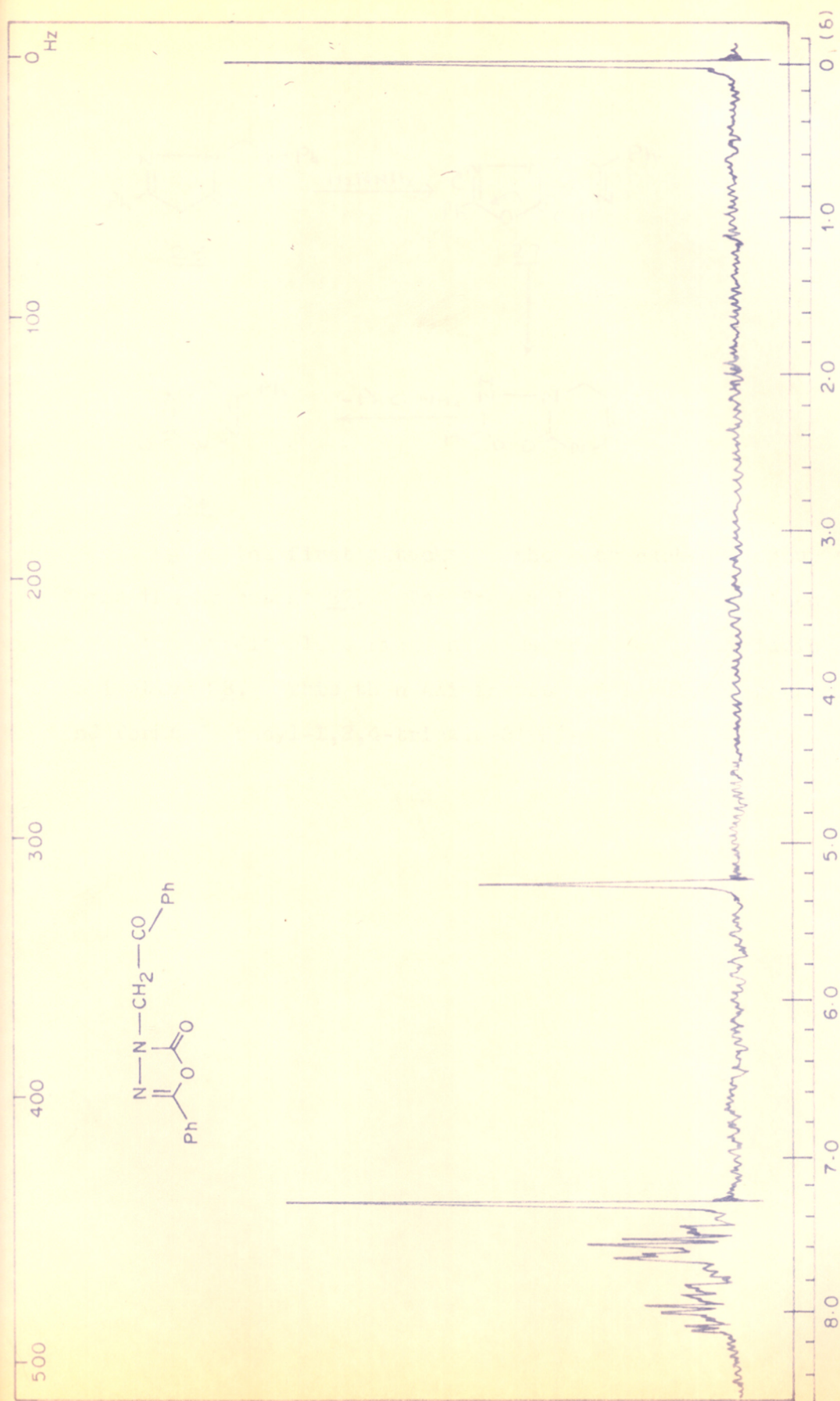
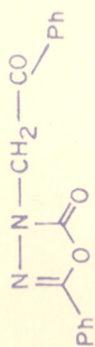
The compound 25 showed M^+ ion at 280 in its mass spectrum. Its IR spectrum showed ring carbonyl frequency at 1785 cm^{-1} along with the side chain carbonyl frequency at 1700 cm^{-1} . In its ^1H NMR spectrum it exhibited a 2H singlet at δ 5.23 for the methylene protons and 10H aromatic multiplets at δ 7.40 - 8.30.

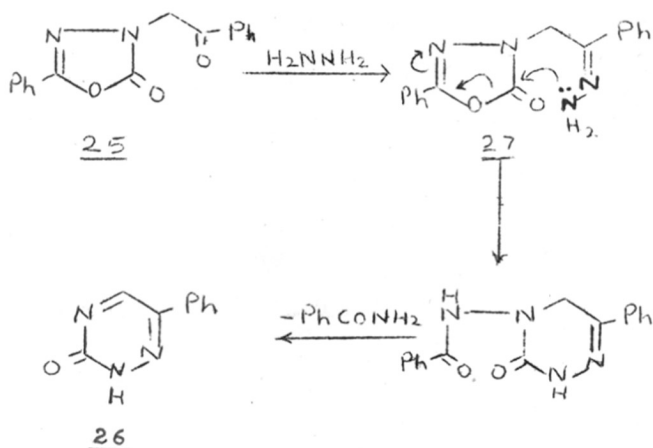
When the compound 25 was refluxed in ethanol containing equimolar amount of hydrazine hydrate (80%), a compound, m.p. 232° was obtained in 25% yield to which structure 26 has been assigned based on its spectral data. It gave satisfactory elemental analyses. Its IR spectrum showed bands at 3500 cm^{-1} for the NH stretching and 1665 cm^{-1} for the amido carbonyl group. Its ^1H NMR spectrum in TFA gave signals only for aromatic protons at δ 7.30 - 7.93. It gave M^+ ion at 173 in its mass spectrum.

The formation of 26 from 25 can be explained according to the following mechanism.



IR OF COMPOUND 25





Hydrazine first attacks at the keto carbonyl group and forms the hydrazone **27**. The free amine group in **27** then attacks C₂ of the oxadiazolone ring and thus produces the triazine derivative **28**. This then eliminates a molecule of benzamide and forms 6-phenyl-1,2,4-triazin-3(2H)-one **26**.

EXPERIMENTAL

Reaction of 3-ethoxycarbonyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one **11** with hydrazine hydrate

Compound **11** (0.234 g; 0.001 M) and hydrazine hydrate (80%) (0.063 g; 0.001 M) were refluxed in ethanol (20 ml) for 4.5 hr. Solvent was then distilled under reduced pressure and the residue was crystallized from benzene containing ethanol to give fine crystals of **13** (0.2 g; 90%).

Compound **13**: m.p. 155° (dec.).

Elemental analyses: Found, C: 48.94%; H: 3.66%; N: 25.57%.

$C_9H_8N_4O_4$ requires, C: 49.09%; H: 3.64%;

N: 25.45%.

IR (ν_{max} ^{nujol}): 1660-1690 (side chain C=O); 1755 (ring C=O); 3500 (NH).

¹H NMR (TFA): 7.26 - 7.83 (m, 5H, aromatic).

Mass: 162 (M^+ - CH_2N_2O).

Thermolysis of **13**

Compound **13** (0.440 g; 0.002 M) was heated in an oil bath at 160° for 20 minutes. The reaction mixture was then extracted with benzene and then benzene evaporated off when the compound **12** was obtained as a white solid (0.225 g; 70%) m.p. 128°.

This solid had superimposable IR, ¹H NMR and Mass spectra and undepressed mixed m.p. with the authentic sample (9).

Reaction of 3-ethoxycarbonyl-5-phenyl-1,3,4-oxadiazol-2(3H)-thione **14** with hydrazine hydrate

Compound **14** (0.250 g; 0.001 M) and hydrazine hydrate (80%) (0.063 g; 0.001 M) were mixed in ethanol (20 ml) and

refluxed for 3 hr. Ethanol was then removed under vacuum. The solid remaining in the flask was then crystallized from aqueous ethanol to needles of 15 (0.130 g; 75%) m.p. 220°.

This had superimposable IR, ¹H NMR and Mass spectra and undepressed mixed m.p. with the authentic sample (10).

Reaction of 3-benzoyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one 17 with nucleophiles

Compound 17 (0.266 g; 0.001 M) and hydrazine hydrate (80%) (0.063 g, 0.001 M) or triethylamine (0.101 g; 0.001 M) were mixed in ethanol (20 ml) and refluxed for 3 hr. Then the solvent was removed and chloroform was added when a solid separated out. It was crystallized from ethanol to fine needles of 19 (0.170 g; 70%) m.p. 235°.

This showed superimposable IR spectrum and undepressed mixed m.p. with the authentic sample (11).

Preparation of 5-phenyl-3-p-toluenesulfonyl-1,3,4-oxadiazol-2(3H)-one 22

Compound 18 (0.950 g; 0.005 M) and p-toluenesulfonyl chloride (0.950 g; 0.005 M) were refluxed in xylene (25 ml) for 40 hr. Then xylene was distilled under reduced pressure. The residue was crystallized from aq. ethanol to fine needles of 22 (1.420 g; 90%).

Compound 22: m.p. 164°.

Elemental analyses: Found, C: 56.77%; H: 3.78%; N: 9.02%.

C₁₅H₁₂N₂O₄S requires, C: 56.96%; H: 3.80%;
N: 8.86%.

$\text{IR}(\nu_{\text{max}}^{\text{nujol}})$: 1790 (C = O).

$^1\text{H NMR}$ (CCl_4): 2.46 (s, 3H, methyl); 7.23 - 8.20 (m, 9H, aromatic).

Mass: 316 (M^+ ion).

Reaction of 22 with nucleophiles

Compound 22 (0.316 g; 0.001 M) and hydrazine hydrate (80%) (0.063 g; 0.001 M) or triethylamine (0.101 g; 0.001 M) were refluxed in ethanol for 5 hr. Ethanol was then removed under reduced pressure. The residue was crystallized from aq. alcohol (0.175 g; 60%) m.p. 163-4°.

This compound gave superimposable IR spectrum and undepressed mixed m.p. with the authentic sample (12).

Preparation of 3-phenacyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one 25

Compound 18 (0.950 g; 0.005 M) and phenacyl bromide (0.995 g; 0.005 M) were mixed and heated at 210° for 1.5 hr. The reaction mixture was then passed through a silica gel column (1:20). Elution with benzene + ethyl acetate (4:1) gave the compound 25 (0.840 g; 60%).

Compound 25: m.p. 146° (pet. ether + CCl_4 mixture).

Elemental analyses: Found, C: 68.44%; H: 4.41%; N: 9.82%.

$\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_3$ requires, C: 68.57%; H: 4.28%;
N: 10.00%.

$\text{IR}(\nu_{\text{max}}^{\text{nujol}})$: 1700 (side chain C = O); 1785 (ring C = O).

$^1\text{H NMR}$ (CDCl_3): 5.23 (s, 2H, methylene); 7.40 - 8.30 (m, 10H, aromatic).

Mass: 280 (M^+ ion).

Reaction of 25 with hydrazine hydrate

Compound 25 (0.280 g; 0.001 M) and hydrazine hydrate (0.063 g; 0.001 M) were refluxed in ethanol (20 ml) for 7 hr. Then the solvent was evaporated off and little chloroform was added. The mixture was cooled overnight when crystals of 26 separated out. It was filtered (0.045 g; 25%).

Compound 26: m.p. 232° .

Elemental analyses: Found, C: 62.67%; H: 4.11%; N: 24.34%.

$C_9H_7N_3O$ requires, C: 62.43%; H: 4.05%;

N: 24.28%.

IR ($\nu_{\max}^{\text{nujol}}$): 1665 (C = O); 3500 (NH).

1H NMR(TFA): 7-30 - 7.93 (m, 7H, aromatic).

Mass: 173 (M^+ ion).

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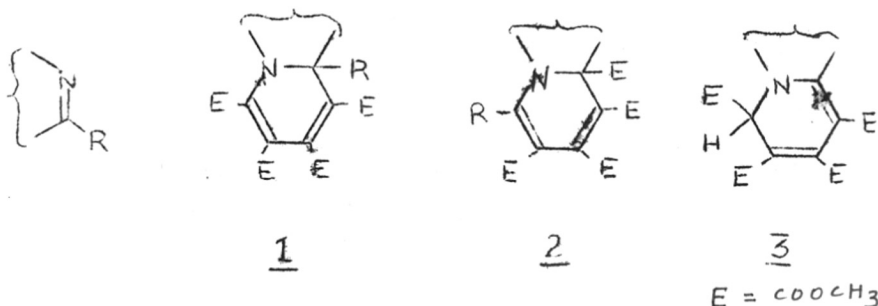
CHAPTER I

Cycloaddition Reactions of Some Triheteroatomic Azoles

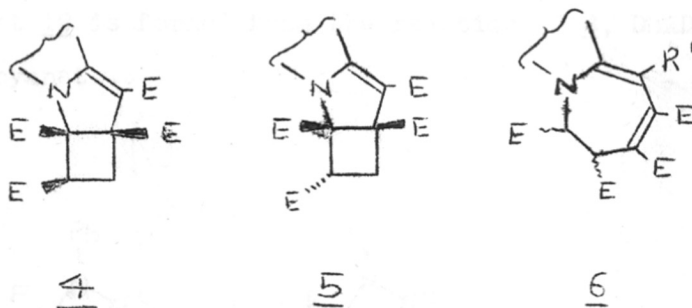
A wide range of heterocyclic compounds containing at least one nitrogen atom and possessing the grouping $-N = C(R)-\bar{R}$ where $\bar{R} = H$ or alkyl as a part of the ring are known to undergo cycloaddition reactions with dienophiles or dipolarophiles such as dimethyl acetylenedicarboxylate (DMAD), phenyl isocyanate, maleic anhydride etc. Especially with DMAD, such cycloaddition reactions have been extensively studied with simple five and six membered heterocycles like pyrrole and pyridine and their fused benzo derivatives as well as with compounds containing two heteroatoms such as thiazole, oxazole, imidazole, pyrazine, pyrimidine, diazine etc. and their corresponding fused benzo derivatives.

Depending on the nature of the heterocycle and reaction conditions, the cycloaddition reactions of the above heterocycles with DMAD can lead to a variety of adducts with structures differing in the degree of complexity and incorporating 2,3 or even 4 moles of DMAD. Such 2:1, 1:1, 1:2, 1:3 and 1:4 cycloadducts have been briefly reviewed.

The 1:2 adducts obtained are of the following types:



When the heterocyclic base contains, at 2-position, an activated methyl or methylene group ($R = -\text{CH}_2-\text{R}'$), besides the above, the following 1:2 type of adducts are also known.



In the present work, the cycloaddition reactions of some 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole derivatives with DMAD and phenyl isocyanate have been studied.

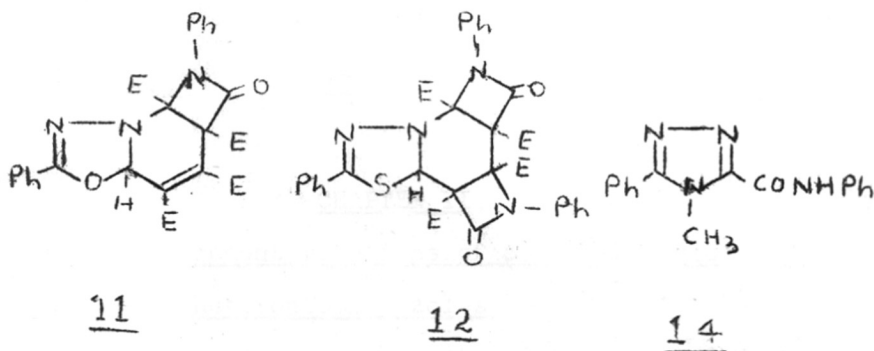
It has been found that both 2-phenyl-1,3,4-oxadiazole 7 and 2-phenyl-1,3,4-thiadiazole 8 at 140° for 3 hr, with DMAD form 1:2 adducts of the type 3.

2-Methyl-5-phenyl-1,3,4-oxadiazole 9 with 1:2 DMAD at 100° for 5 hrs gives the 1:2 adduct of type 6 and a crude mixture of 1:3 red adducts (indicated by M^+ in Mass Spectrum). However,

the crude 1:3 adduct mixture could not be purified either by chromatography or by crystallization.

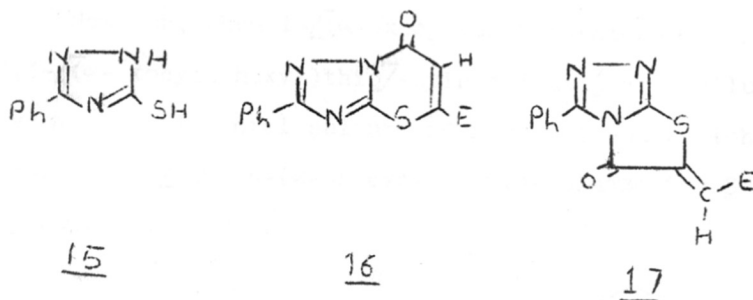
2-Methyl-5-phenyl-1,3,4-thiadiazole 10, on the other hand at 100° for 3 hrs, with DMAD gives a product of type 6 and a product of type 2. When this reaction is carried out at room temperature for 5 days in DMF, two isomeric compounds of the type 6 (n.p. 72° and 171°) are formed along with the 1:2 adduct of type 2.

A novel type of 1:2:1 adduct has been isolated from the reaction of 7, DMAD and phenyl isocyanate. Based on the spectral data, it has been assigned the structure 11. Another interesting 1:2:2 adduct 12 is formed from the reaction of 8, DMAD and phenyl isocyanate.



4-Methyl-3-phenyl-1,2,4-triazole 13 reacts with DMAD even at -35°, but no definite cycloadduct could be isolated in the pure form from the highly complex reaction mixture. With phenyl isocyanate, on the other hand, 13 forms a smooth 1:1 adduct 14 in more than 90% yield, similar to pyrazoles and imidazoles.

Recently Srinivasan and Upadhyaya reported that 3-mercapto-5-phenyl-1,2,4-triazole 15 reacts with DMAD in refluxing methanol containing glacial acetic acid to give 16 m.p. 196° . An isomeric compound, m.p. 197° has been isolated by carrying out the reaction in methanol containing a few drops of hydrochloric acid at room temperature for 24 hours. Based on the spectral data (particularly ^1H NMR) and recent correction in structures of addition products formed from thioureas and DMAD from thiazinone to thiazolinone structures by X-ray crystallography, structure 17 has been proposed for the above addition product.

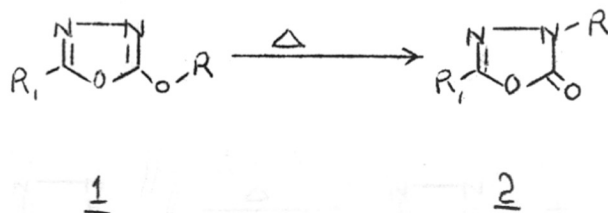


CHAPTER II

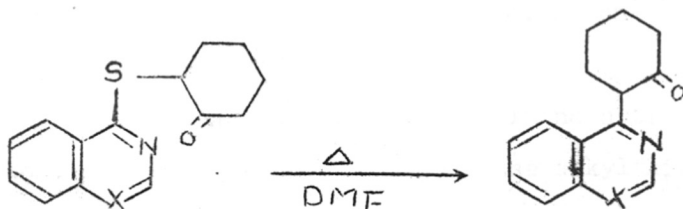
Thermal rearrangement reactions of some alkylthio substituted triheteroatomic azoles

Many thermal rearrangement reactions involving 1,3-alkyl migrations are known in the literature. The various types of thermal 1,3 alkyl migration reactions have been briefly accounted. It is observed that very few examples of 1,3 S $\rightarrow$ N alkyl migration reactions exist in the literature.

Inino ethers are known to thermally rearrange into their corresponding N-substituted amides. Thus Golfier et al. reported that 2-alkoxy-1,3,4-oxadiazoles rearrange on heating to their corresponding 3-alkyl-1,3,4-oxadiazol-2(3H)-ones 2.



However, when 1-[α -oxocyclohexyl]thio-isoquinoline 5 and 4-[α -oxocyclohexyl]thio-quinazoline 6, are refluxed in DMF, they extrude elemental sulfur and form 1-(α -oxocyclohexyl)-isoquinoline 7 and 4-(α -oxocyclohexyl)-quinazoline 8 respectively.



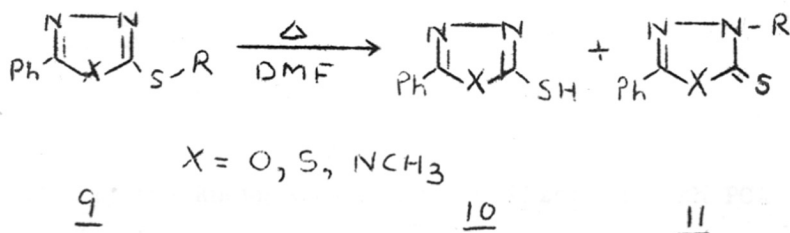
5: X = CH

6: X = N

7: X = CH

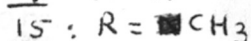
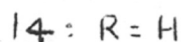
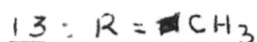
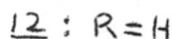
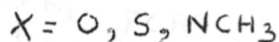
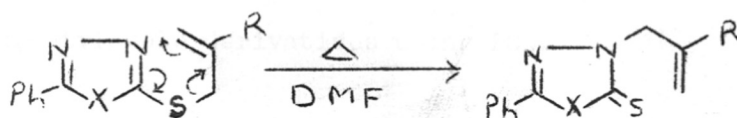
8: X = N

The present work comprises of a study of the thermal rearrangement reactions of alkylthio substituted triheteroatomic azoles for attempted sulfur extrusion reactions. It has been found that in refluxing DMF, the β -ketoalkylthio substituted triheteroatomic azoles 9 yield mercapto azoles 10 along with N-alkyl thiones 11 formed by 1,3 S $\rightarrow$ N migration of alkyl group.



It has been observed that when the alkyl group contains a keto group at the β -position, the carbonyl frequency of N-alkyl-thiones 11 comes higher by ca. 25 cm^{-1} than that of corresponding alkylthio azoles 9.

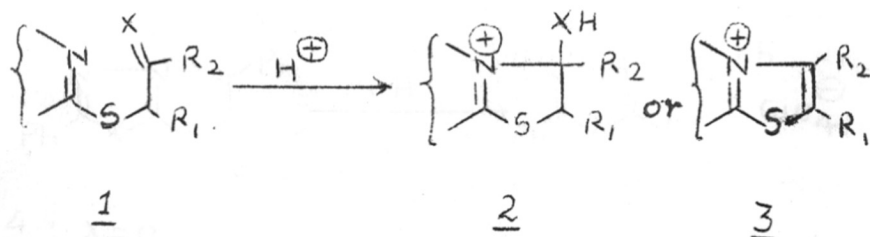
Based on the tendency of the imino nitrogen atom in 9 to abstract a β -hydrogen atom from the alkylthio group and thus form 10, the thio-Claisen rearrangement reactions of allylthio 12 and methallylthio 13 substituted triheteroatomic azoles were carried out. These reactions went very smoothly producing over 80% yields of N-allyl 14 and N-methallyl 15 thiones respectively.



CHAPTER III

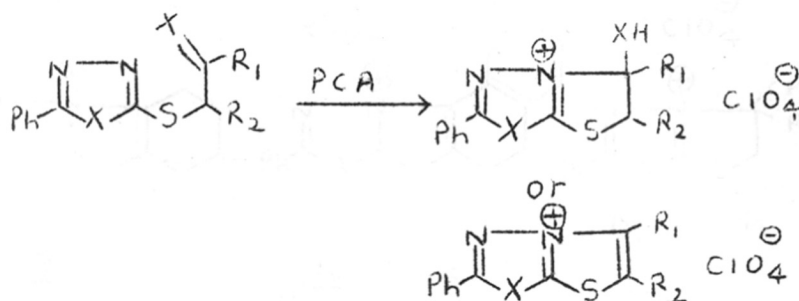
Synthesis of fused triheteroatomic azole ring systems

Many heterocyclic imino alkylthio ethers of the type 1, in which the alkyl group contains a β -keto grouping or β - γ unsaturation, are known to undergo cyclization with PCA to form 2 and cyclodehydration with acids like sulfuric acid, polyphosphoric acid or hydrobromic acid to produce 3.

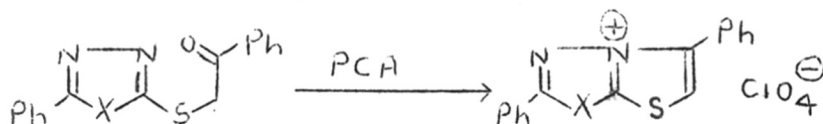


These types of reactions have been studied for many heterocyclic systems like pyridines, quinolines, phenanthridines, pyrimidines, pyrazines, thiazoles, benzothiazoles, triazoles, tetrazoles etc. All attempts to cyclize the benzoxazole derivative failed.

In the present work these types of reactions have been carried out with some (β -keto or β - γ unsaturated) alkylthio substituted 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole derivatives using PCA.



It was observed that 2-phenacylthio-5-phenyl-1,3,4-oxadiazole 4 did not react with PCA at 100° for 15 hr. while the corresponding 1,3,4-thiadiazole and 1,2,4-triazole derivatives 5 and 6 were smoothly cyclodehydrated with PCA at 100° to form 7 and 8 respectively.



4 : $X = O$

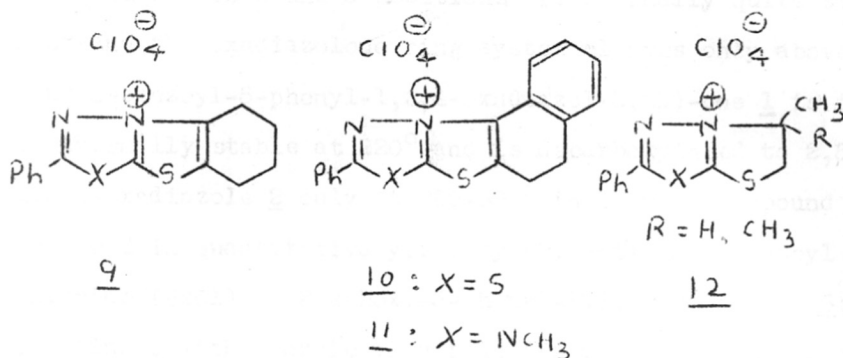
5 : $X = S$

6 : $X = \text{NCH}_3$

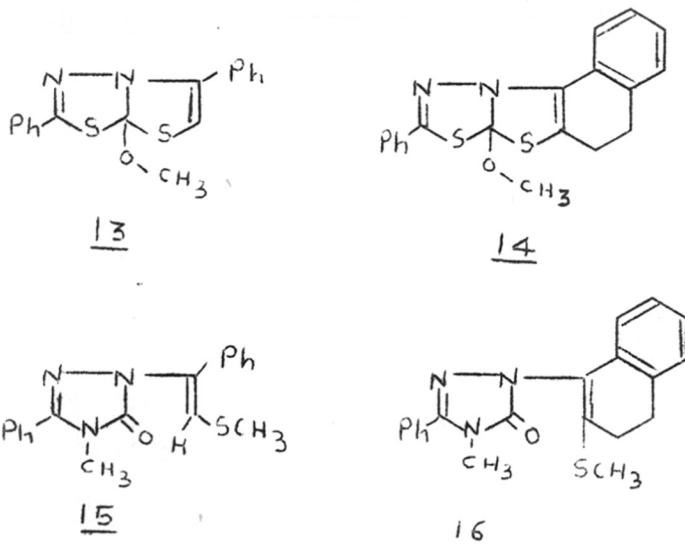
7 : $X = S$

8 : $X = \text{NCH}_3$

In a similar way using appropriate alkylthio substituted 1,3,4-thiadiazoles and 1,2,4-triazoles, the following ring systems were also prepared.



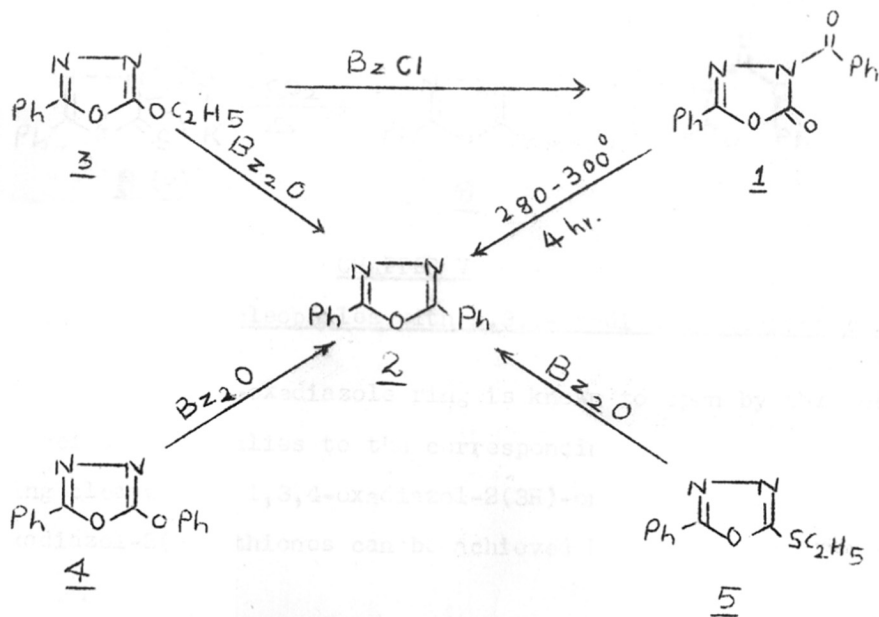
It was found that the fused 1,3,4-thiadiazolium salts 7 and 10 reacted with methanolic KCN and formed the compounds 13 and 14 respectively. However, the ring opened compounds 15 and 16 were obtained from a similar reaction with the 1,2,4-triazolium salts 8 and 11 respectively.



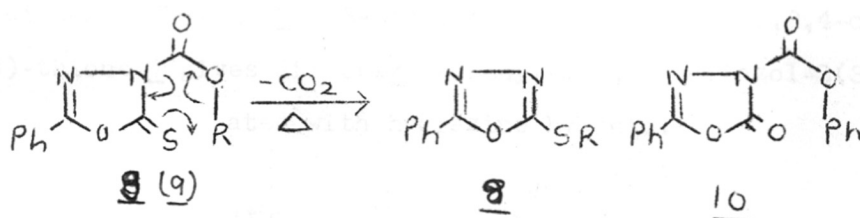
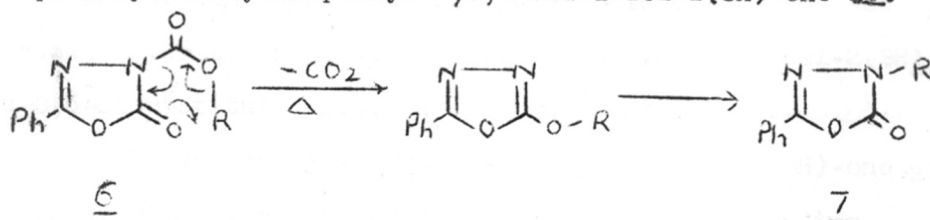
CHAPTER IV

Thermal Rearrangement of 1,3,4-oxadiazole derivatives

The 1,3,4-oxadiazol-2(3H)-ones with alkyl or aryl substituents in 3 and 5 positions are thermally quite stable at 220° and the oxadiazolone ring system cleaves only above 250°. Thus, 3-benzoyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one 1 is found to be thermally stable at 220° and is decarboxylated to 2,5-diphenyl-1,3,4-oxadiazole 2 only at 280-300° in 4 hrs. Compound 1 was prepared in quantitative yield by the action of benzoyl chloride (BzCl) on 2-ethoxy-5-phenyl-1,3,4-oxadiazole 3; but treating 3 with benzoic anhydride (Bz₂O) gave 2 as a major product. A mechanism for the formation of 2 from 3 involving OBz⁻ ion has been proposed. This was supported by the formation of 2 from 2-phenoxy-5-phenyl-1,3,4-oxadiazole 4 and Bz₂O as well as from the reaction of 2-ethylthio-5-phenyl-1,3,4-oxadiazole 5 and Bz₂O.



On the basis of thermal stability of 1,3,4-oxadiazol-2(3H)-one ring system, a revised mechanism (not involving cleavage of the ring system as proposed by Golfier et al.) involving a six membered transition state has been proposed for the thermal conversion of 3-alkoxycarbonyl-5-phenyl-1,3,4-oxadiazol-2(3H)-ones 6 to 3-alkyl-5-phenyl-1,3,4-oxadiazol-2(3H)-ones 7 with a net loss of CO_2 . This mechanism is supported by the thermal formation of 2-ethylthio-5-phenyl-1,3,4-oxadiazole 8 from 3-ethoxycarbonyl-5-phenyl-1,3,4-oxadiazol-2(3H)-thione 9 as well as the thermal stability of 3-phenoxy-carbonyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one 10.

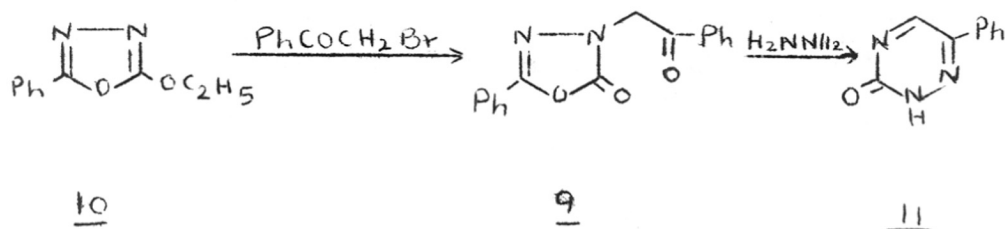


CHAPTER V

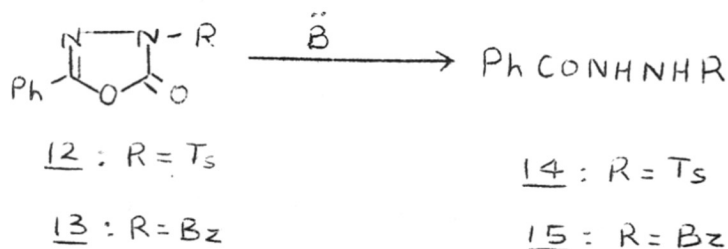
Reactions of Nucleophiles with 1,3,4-oxadiazole derivatives

The 1,3,4-oxadiazole ring is known to open by the action of acids and alkalis to the corresponding dihydrazides. The ring cleavage of 1,3,4-oxadiazol-2(3H)-ones and 1,3,4-oxadiazol-2(3H)-thiones can be achieved by the action of

on treatment with hydrazine hydrate yields 6-phenyl-1,2,4-triazin-3(2H)-one 11. A mechanism for the formation of 11 from 9 has been proposed.



3-Tosyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one 12 and 3-benzoyl-5-phenyl-1,3,4-oxadiazol-2(3H)-one 13, similarly prepared, reacted with hydrazine hydrate and triethylamine to give their corresponding ring opened dihydrazides 14 and 15 respectively.



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G.S. Shirwaiker

NCL, Poona-8

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